History of Transplantation: Thirty-Five Recollections

Paul I. Terasaki, *EDITOR*

1868

THE LIBRARY
OF
THE UNIVERSITY
OF CALIFORNIA
LOS ANGELES

GIFT OF

Dean Sherman M. Mellinkoff

2007

Sherman Mellinkoff

History of Transplantation: Thirty-Five Recollections

G. P. J. Alexandre
D. Bernard Amos
Fritz H. Bach
Christiaan N. Barnard
Folkert O. Belzer
Rupert E. Billingham
Leslie Brent
Sir Roy Calne
Raffaello Cortesini
John B. Dossetor
E. J. Eichwald
Willard E. Goodwin
Jean Hamburger
David M. Hume*
Willem J. Kolff &
  Satoru Nakamoto
Samuel Kountz*
René Küss
H.M. Lee
Sir Peter Medawar*
Anthony P. Monaco
Peter J. Morris
Joseph E. Murray
John S. Najarian
Rudolf Pichlmayr
Felix T. Rapaport
Keith Reemtsma
Paul S. Russell
Norman E. Shumway &
  Richard R. Lower &
  Eugene Dong
George D. Snell
Thomas E. Starzl
Paul I. Terasaki
E. Donnall Thomas
Dirk van Bekkum
Jon J. van Rood
Sir Michael Woodruff

*Deceased

Published by
UCLA Tissue Typing Laboratory
1000 Veteran Avenue
Los Angeles, California 90024

Books published by the UCLA Tissue Typing Laboratory
1000 Veteran Avenue
Los Angeles, California 90024

Clinical Kidney Transplants 1985
Clinical Transplants 1986
Clinical Transplants 1987
Clinical Transplants 1988
Clinical Transplants 1989
Clinical Transplants 1990
History of HLA: Ten Recollections
(All volumes still available)

©1991 The Regents of the University of California

ISBN 0-9604606-7-5

No part of this book may be reproduced, stored in a retrieval system, or transmitted in any form by any means, electronic, mechanical, photocopying, microfilming, recording, or otherwise without written permission from the publisher.

Biomed
Hist Div
WO
11.1
H673
1991

Table of Contents

Page

Sir Peter B. Medawar
By L. Brent, R. Billingham, A. Mitchison. L. Thomas, and D. Pyke 1

George D. Snell
A Geneticist's Recollections of Early Transplantation Studies 19

René Küss
Human Renal Transplantation Memories, 1951 to 1981 37

Jean Hamburger
Memories of Old Times 61

Rupert E. Billingham
Reminiscences of a "Transplanter" 73

Leslie Brent
Tolerance and GvHD: An Exciting Decade 93

David M. Hume
As Remembered by H.M. Lee..111

Joseph E. Murray
Nobel Prize Lecture: The First Successful Organ Transplants in Man............... 121

Thomas E. Starzl
My Thirty-five Year View of Organ Transplantation 145

Sir Michael Woodruff
Transplantation: A Personal Recollection.. 183

Ernst J. Eichwald
Episodes of the Early Years 199

Willard E. Goodwin
Early Experiences in Kidney Transplantation... 215

Sir Roy Calne
Recollections from the Laboratory to the Clinic.. 227

Willem J. Kolff and Satoru Nakamoto
The Reestablishment of Cadaver Kidney Transplantation:
Early Kidney Transplantation at the Cleveland Clinic: 245

H.M. Lee
Recollections 267

John B. Dossetor
Transplantation: A Canadian Career-Giving Experience 293

Paul S. Russell
Some Personal Reflections on the Development of Transplantation 307

G.P.J. Alexandre
From the Early Days of Human Kidney Allotransplantation to Prospective Xenotransplantation 337

Felix T. Rapaport
The Life and Times of a Transplant Immunosurgeon 349

E. Donnall Thomas
Allogeneic Marrow Grafting: A Story of Man and Dog 379

Dirk W. van Bekkum
Bone Marrow Transplantation: A Story of Stem Cells 395

Norman E. Shumway, Richard R. Lower, and Eugene Dong
A Heart Transplantation Narrative: The Earliest Years 435

John S. Najarian
A Transplant Odyssey 451

D. Bernard Amos
A Theoretical and Experimental Approach to Transplantation: The Duke Experience 475

Paul I. Terasaki
Histocompatibility 497

Jon J. van Rood, A. van Leeuwen, and J.G. Eernisse
The Eurotransplant Story 511

Fritz H. Bach
Recollection 539

Keith Reemtsma
Reflections of a Xenotransplanter 553

Christiaan N. Barnard
The First Human-to-Human Heart Transplant 565

Samuel L. Kountz
As Remembered by K. Butt and F.O. Belzer 585

Folkert O. Belzer
Organ Preservation: A Personal Perspective 595

Anthony P. Monaco
Personal Memory of Antilymphocyte Serum and Its Impact on Transplantation 615

Peter J. Morris
Transplantation: Personal Recollections 637

Rudolf Pichlmayr
History of Transplantation 659

Raffaello Cortesini
An Overview of the Evolution of Transplantation: A Personal Experience 675

Participants at the David M. Hume Memorial Symposium on Transplantation in Richmond, Virginia, April 1974.

Front row (L-R): J. Merrill, S. Kountz, F. Moore, K. Porter, G.M. Williams, H.M. Lee, J. Pierce;
Second row (L-R): W. Lawrence, R. Schwartz, D.W. van Bekkum, J.E. Murray, T.E. Starzl, E.D. Thomas, F.O. Belzer, P.I. Terasaki, R. Billingham, R. Bachvaroff;
Third row (L-R): F.P. Stuart, J.S. Wolf, R.R. Lower, J.S. Najarian, D.B. Amos, J.A. Mannick, J. Hamburger, H. Balner, J.H. Harrison, R.Y. Calne.

PREFACE

Transplantation is the miracle of 20th century medicine. This startling development occurred in a relatively short space of time, in two short decades of the 1950s and 60s. From impossibility in the early 50s, the field exploded into today's clinical therapy.

Gathered in this volume are personal recollections from thirty-five key pioneers of transplantation who were vitally involved during this narrow window of time. Each author was free to offer his own story and all chapters are published in their unexpurgated form, for I did not feel qualified to edit the writings of my colleagues, many of whom are editors of journals themselves.

Although this is not meant to be a traditional transplantation history book, these subjective reminiscences are intended to convey the story from the vantage points of the individual participants as the drama unfolded. The perceptive reader can compare chapters for differing versions of the same events and glean a broad understanding of how the phenomenon developed from these individual accounts of the early investigators.

We hope these delightful stories of adventure, mishaps, disappointments, and glories which were part of this international quest will make for very enjoyable reading. One can also note the extensive interaction among the rival comrades - each operating within the influential sphere of the others. Many were the conferences during which new findings were shared freely worldwide. Extensive personal contacts and exchanges of personnel among the groups are evident from the chapters, demonstrating so vividly that mastery over the early problems of transplantation was truly an international scientific achievement!

No doubt many objective accounts of this story will appear in the future, and historians should find this to be a rich source material, prepared now as most of the workers advance to retirement and beyond. In fact, three of the chapters have been written about members who are no longer with us. For the first generation trailblazers, this undertaking could wait no longer.

The order of presentation is a rough approximation of the time frame within which each author's main contribution came to light. Interestingly, the seminal events, for the most part, occurred mainly in the decade of the 1960s. The many advances since then hopefully will be the subject of a subsequent installment.

The international conferences that played such a vital role in the development of the field are listed on the next page. The photo taken at the David Hume Memorial Symposium includes many of the authors of this book.

I am indebted to Jane Schoenberg, principal editor, Su-Hui Lee, Dan Davis, Rita Loew, Beverly Looman, Ed Sato, Joyce Yuge, Jennifer Kawata, Kirk Chang, Lupita Geer, and Elizabeth Siauw for their wonderful help in putting together what I hope is a unique volume.

Paul I. Terasaki
May 20, 1991

NEW YORK ACADEMY OF SCIENCES MEETINGS ON HOMOTRANSPLANTATION

	DATE	LOCATION	ORGANIZERS
I.	Feb. 1954	New York	J.M. Converse, B. Rogers
2.	Feb. 1956	New York	J.M. Converse, B. Rogers
3.	Oct. 1958	New York	J.M. Converse, B. Rogers
4.	May 1960	New York	J.M. Converse, B. Rogers
5.	Oct. 1962	New York	J.M. Converse, B. Rogers
6.	Nov. 1964	New York	J.M. Converse, B. Rogers, F. Rapaport
7.	Dec. 1966	New York	J.M. Converse, F. Rapaport, F. Dausset

MEETINGS OF THE INTERNATIONAL CONGRESS OF THE TRANSPLANTATION SOCIETY

	DATE	LOCATION	PRESIDENT	ORGANIZERS
I.	June 1967	Paris, France	Sir Peter B. Medawar	J. Dausset J. Hamburger G. Mathé
II.	June 1968	New York, New York	John Marquis Converse	John Marquis Converse Felix T. Rapaport
III.	Sept. 1970	The Hague, The Netherlands	Jean Hamburger	D.W. van Bekkum J.J. van Loghem J.J. van Rood
IV.	Sept. 1972	San Francisco, California	Paul S. Russell	Samuel L. Kountz Rupert E. Billingham
V.	Aug. 1974	Jerusalem, Israel	Sir Michael Woodruff	Rupert E. Billingham Michael Schlesinger
VI.	Aug. 1976	New York, New York	Rupert E. Billingham	Felix T. Rapaport Jean Marquis Converse
VII.	Sept. 1978	Rome, Italy	Leslie Brent	Raffaello Cortesini Hans Balner
VIII.	June 1980	Boston, Massachusetts	Felix T. Rapaport	Anthony P. Monaco Mary L. Wood
IX.	Aug. 1982	Brighton, United Kingdom	Hans Balner	Leslie Brent
X.	Aug. 1984	Minneapolis, Minnesota	Paul I. Terasaki	John S. Najarian Fritz H. Bach
XI.	Aug. 1986	Helsinki, Finland	Peter J. Morris	Pekka Häyry Saija Koskimies
XII.	Aug. 1988	Sydney, Australia	Anthony P. Monaco	A.G. Ross Sheil
XIII.	Aug. 1990	San Francisco, California	J. Richard Batchelor	Oscar Salvatierra, Jr. Edward Stinson Norman Shumway

Sir Peter B. Medawar

1915 - 1987

Written by Leslie Brent, Rupert Billingham,
Avrion Mitchison, Lewis Thomas, and David Pyke

Sir Peter Medawar

Sir Peter B. Medawar

AN OUTSTANDING CONTRIBUTION TO MEDICAL SCIENCE
(an obituary that appeared in *The London Times* on October 5, 1987)

Sir Peter Medawar, OM, CH, CBE, FRS, died on October 2, at the age of 72. Although his career was cruelly disrupted by illness when he was only 54, he was one of the outstanding scientists of his generation. He won the Nobel Prize in 1960 for his research on tissue grafting, which is basic to organ transplants.

Peter Brian Medawar was born in Rio de Janeiro on February 28, 1915, to an English mother married to a Lebanese businessman. He was sent to England for his education, which included Marlborough and Magdalen Colleges, Oxford. He was unhappy at Marlborough and he later spoke disparagingly of its sexual and intellectual climate in those days.

He took a first in zoology at Oxford, where he was much influenced by Professor Howard Florey. In Florey's department he met Jean Taylor, a fellow student. They married in 1937.

Medawar's early work was on the regeneration of nerves, but the studies that proved to have the most profound influence were in the field of tissue grafting. It was largely thanks to his experiments with rabbit skin grafts that the immunological basis of graft rejection became accepted.

The impetus for this work stemmed directly from the war, for the Medical Research Council had recognized that more effective means than those available at the time were needed for the treatment of severe burns. Among his earliest publications was a study carried out with a Scottish surgeon, Thomas Gibson, on the rejection patterns of human skin grafts.

In 1947 Medawar accepted the Chair of Zoology at Birmingham University. In 1951, he was invited to become Jodrell Professor of Zoology at University College, London, where he stayed until 1962, when he became Director of the National Institute for Medical Research.

His close collaborators were Rupert Billingham and Leslie Brent. This team produced a series of incisive and elegant scientific publications that ushered in the era of cellular immunology - the main preoccupation of immunologists having been, up to then, with the blood-borne antibodies that are frequently the end-product of immunological responses. Now attention was focused on cells, in particular lymphocytes, that Medawar and his collaborators showed to be closely associated with graft rejection and other immunological phenomena.

The most significant contribution by Medawar's group - for which he won his Nobel Prize, jointly with the Australian immunologist, Sir MacFarlane Burnet - was the demonstration that graft rejection can be entirely prevented in mice and chickens if foreign cells from the future donor are introduced into the recipient during foetal or neonatal life (that is, at a time when the animals are still immunologically immature).

The theoretical framework that led to this study had several sources: the long known observation that cattle fraternal twins have a common intra-uterine blood circulation; Dr. R.D. Owen's demonstration in the United States that such twins exchange red blood cells and their precursors *in utero* and possess each other's red blood cells in adult life; the finding by Medawar's own group in Birmingham that skin grafts exchanged between fraternal non-identical twin calves are not rejected; and the brilliant speculations by MacFarlane Burnet and

Frank Fenner on the concept of "self" and "non-self".

Medawar's group set about showing that immunological unresponsiveness can be established experimentally and that it is highly specific for the donor's tissue antigens. Although it was later shown that the mechanism underlying this phenomenon is not quite as straightforward as their experiments had led them to believe, the impact of the discovery was dramatic.

First, it was a clear demonstration that the immunological barriers to the transplantation of foreign tissue and organ grafts - thought to be insurmountable - could be overcome by subtle immunological interference, rather than by the blunderbuss approach of whole body X-irradiation or antimitotic drugs, and it opened up a vast new field of scientific endeavour. Second, it provided an insight into why the body does not normally respond to its own cellular substances and what happens when it does, as for example in patients suffering from autoimmune disease. And third, it directly led to the discovery by Billingham and Brent of graft-versus-host disease, a condition caused by the presence of mature lymphocytes in certain kinds of grafts. Even now this poses considerable clinical problems in the transplantation of bone marrow.

On his move to the National Institute for Medical Research Medawar combined the duties of Director with his research interests. He had a succession of bright young colleagues, and the flow of innovative scientific publications continued unabated.

Then, in 1969, came the grievous blow. He was at the time President of the British Association, which was meeting in Exeter, and whilst reading the lesson during the Sunday service in the cathedral he suffered a brain hemorrhage that left him seriously handicapped for the remainder of his life.

A few years later he gave up his directorship and moved to the Clinical Research Centre in Northwick Park, where he maintained a small research group and turned his attention away from tissue transplantation to the problem of cancer. It was his hope that he might be able to devise a cancer vaccine - another typically audacious objective he set himself. In this instance his hopes may, however, have been less realistic and they have yet to be realized.

Medawar was the international leader in his field and he inspired his research teams with his infectious enthusiasm, and by example. He loved nothing better than to work with his own hands in the laboratory. He was also an inspiring lecturer and writer.

His earlier critical essays were published as monographs (*The Uniqueness of the Individual*, *The Art of the Soluble*, *A Hope of Progress*, for example) and are classics of their kind. Although his later books tended to be more eclectic (*The Life Science*, and *From Aristotle to Zoos*, both with Lady Medawar; *Advice to a Young Scientist*, and most recently, *Pluto's Republic*) they continue to have a wide readership.

His last book was the widely acclaimed *Memoirs of a Thinking Radish* (1986), an account of some aspects of his life and scientific endeavours. In it he described with great detachment and humour what it is like to be physically handicapped, avoiding self-pity and being careful not to reveal too much of himself.

Like many other great men Medawar brought his vast talents to bear on subjects peripheral to his main endeavours. For example, he had a deep and lasting interest in philosophy and he was much influenced by Sir Karl Popper, who became a close friend. In his writings, as in his lectures, he discussed the methods and limitations of science and the place of science in society. He disdained all manifestations of 'Naturphilosophie' and his devastating critique of Pierre Teilhard de Chardin's book, *The Phenomenon of Man*, displays all his analytical powers.

Medawar was much in demand on public bodies. He was the first President of The (International) Transplantation Society in 1966 and he became President of the British Association in 1969, as well as a member of the Governing Body of the BBC. He delivered the Reith lectures in 1959 on "The Future of Man".

Virtually every honour that the academic world can bestow came his way. He was an FRS at 34, and was awarded honorary degrees by a score of universities all over the world. He was knighted in 1965, made a Companion of Honour in 1972 and made a Member of the Order of Merit in 1981.

Medawar was a man without a trace of pomposity and with a mischievous sense of humour, even in his darkest days. He delighted in conversation (whether accompanied by ale in a pub or claret in his home) and relished village cricket. He was a keen squash player until his paralysis put a stop to his sporting activities.

Almost to the end he indulged in his other hobbies of chess and music. He was an ardent lover of opera, with a particular passion for Wagner and Verdi.

One of the most extraordinary aspects of his life was the way he coped with his severe afflictions. New setbacks were met with an unflagging determination that life must go on.

Medawar is survived by two daughters and two sons, and by his wife, Jean, whose devoted support and encouragement was such a crucially important feature of his life, particularly during the last exacting years.

SIR PETER MEDAWAR OM CH

(reprinted from the obituary written by L. Brent, first published in *The Independent* [London] on October 5, 1987)

By the time that Peter Medawar left University College London to become Director of the National Institute for Medical Research in 1962, he had already established himself as a towering pioneer. His work led not only to a far clearer understanding of the immunological basis of tissue and organ graft rejection, but to the creation of the now vast and complex field of cellular immunology.

His achievements had been marked by a succession of honours (including the Nobel Prize for medicine in 1960) that continued unabated until his death (the latest and much cherished being the renaming of his University College department the "Medawar building").

What made him one of the greatest, and most charismatic, scientists of his generation? What made him turn to biology? He had disliked his schooldays at Marlborough intensely, but it was there that his keen intellect and powerful analytical mind were committed to biology, thanks to the ministrations of his biology master. Biology suited him, because in the mid-Forties (long before Crick and Watson had unravelled the structure of DNA) it was still a field in its infancy. Traditionally it had concentrated on comparative anatomy and physiology, population genetics, evolutionary theory and the interaction of organisms with their environment: there was plenty more to be discovered. Medawar was immediately attracted by the notion that it should be possible to study the cells and molecules within the body, with a view to solving problems that both presented an intellectual challenge and had clinical relevance.

Peter Medawar was an experimental scientist *par excellence*: he loved nothing better than to work at the bench, doing experiments on his own or in collaboration. Although an imposingly tall man, with largehands, he carried out precise and delicate manipulations with impressive deftness. Doing experiments, as opposed to watching others perform them, was a vital part of his creativity. Coupled with this was an outstandingly incisive and untrammelled mind that rejected the trivial and the pedantic and that was forever open to new ideas and hypotheses.

He had an enviable talent as a communicator, whether on the written page or through the spoken word; his lectures, including those to undergraduates, were never less than riveting. Few young immunologists regard scientific papers written more than 10 years ago as worth reading; but many of Medawar's early papers are classics and impress the reader not only by the importance of their findings but equally by the elegance and lucidity of their prose.

His second collection of essays, published in 1967, was *The Art of the Soluble*. One of the secrets of his success as an experimenter was that he asked questions that were in principle open to analysis, given the prevailing knowledge and technique. His equipment tended to be astonishingly simple: what mattered most was the design and execution of experiments. Yet he took a boyish delight in any new piece of equipment, proudly putting his first high-speed centrifuge through its paces for the benefit of anyone who cared to watch and who was willing to make appropriate admiring noises.

The 14 years in which I worked closely with him in the laboratory will remain for me (and for our colleague Rupert Billingham, too) an unforgettable and exciting experience. Peter Medawar likewise thought of the Fifties as his most exhilarating period of research: but then it was in the Fifties that the phenomenon of immunological tolerance was discovered.

During his stewardship, the Department of Zoology at University College London housed an extraordinary array of talent. Many of its members were later appointed to university chairs in the UK or the United States, and at least four became Fellows of the Royal Society. Two Emeritus Professors, D.M.S. Watson and J.B.S. Haldane, continued to work in the department for many years, thus contributing to its intellectual richness.

One of Medawar's great strengths was that he gave encouragement to talented eccentrics and especially to the young. He had a way of infecting others around him with his own enthusiasm and *joie de vivre*. This was true not only in research, but in the many extra-mural activities that enriched his life. He played village-type cricket for his department and later for his institute with enormous zest, was a relentless and skillful opponent at squash, and played chess with great panache ("Ah, a brilliancy!"). Dinner at the Athenaeum was usually followed by a hilarious game of snooker in the then cavernous billiards room.

His most abiding love was music, especially opera, and long before Janácek became known in this country he introduced me to this composer by saying one day, "let's go and hear *Jenufa* at Covent Garden tonight": we did. His intimate knowledge of many operas, especially those of Wagner and Verdi, was most impressive; the emotions they portrayed were very real to him and he was fond of saying that he would most like to have been a *Heldentenor*.

Did this extraordinary man have no faults at all, then? He had a passionate and, I suspect, unjustified contempt for Freud's theories, mainly because they cannot be substantiated by the scientific method. In his formidable prime he could speak dismissively of people who did not engage his interest. And like other highly creative and outstanding scientists he found it difficult to devote enough time to his four children when they were young, something that he came to regret in later life.

It is 18 years since Peter Medawar suffered his first stroke, from which he never fully recovered. Several more were to follow, steadily increasing the severity of his handicap. Yet neither he nor his family ever gave up. He was exceptionally fortunate in having, in Jean, a widely talented wife who brought great love and intelligence to bear in devoting boundless determination, care and physical energy to his recovery and to making sure that life did not lose its value for him, even in his days of grievous affliction. The support of his four children and their families was invaluable in encouraging his own efforts to recover, as was the continued contact with his wide circle of friends.

During those years he mellowed and allowed his sense of humour to develop a warmer quality. The good humour and awesome stoicism with which he bore his misfortune was one of the most striking features of his last years. It was during this difficult period too that most of his books were written, all of which continue to delight his readers with their wisdom, wit and felicity of phrase.

-Leslie Brent

Peter Medawar was the most distinguished British biologist of his generation, writes N.A. Mitchison.

He founded the modern scientific study of the rejection of transplants of tissue. By examining skin grafts in rodents and man he discovered that rejection is brought about by an immunological response on the part of host lymphocytes against "histocompatibility" antigens on the cells of the graft. This and further discoveries on the same subject provide a key part of the present science of immunology. Immunology today has strong roots in genetics and molecular biology, and it is easy to forget Medawar's work on the accelerated rejection of second-set grafts, the immunologically reactive cell, cell-mediated immunity, and immunosuppressive antibodies. The new branch of science that he founded has produced great benefits in medicine and surgery, of which far the most important is the successful transplantation of the kidney, the heart, and other organs and tissues. Transplantation biologists look forward to other successes in the future, notably the treatment of diabetes by transplantation of the pancreas itself.

Medawar's greatest single discovery, made jointly with colleagues in his own team and abroad, was of immunological tolerance: the immune system is not preprogrammed to distinguish between self and non-self, but learns to do so as a result of exposure to self-molecules during early development. This principle helps us to understand how the immune system is shaped, helps establish the working of clonal selection among lymphocytes, and leads on to a rational understanding of autoimmune disease. For it, he shared the Nobel Prize for Medicine in 1960.

Just as his scientific life dispels the notion of any gulf between pure and applied science, so the principal message of his 10 beautifully written, lucid, and immensely popular books dispels any idea that the doings of scientists are obscure or mysterious. There is some irony in the fact that the man whose best-loved essay asks "Is the scientific paper a fraud?" was himself a supreme artist of the scientific paper.

Peter Brian Medawar, medical scientist, born 28 February 1915, Mason Professor of Zoology Birmingham University 1947-51, Jodrell Professor of Zoology and Comparative Anatomy University College London 1951-62, Director National Institute for Medical Research 1962-71, Director Emeritus 1975, MRC External Scientific Staff 1971-84, Clinical Research Centre 1984-86, FRS 1949, CBE 1958, CH 1972, OM 1981, publications include The Uniqueness of the Individual (1957), The Future of Man (1960), The Art of the Soluble (1967), Advice to a Young Scientist (1979), Pluto's Republic (1982), Aristotle to Zoos (with J.S. Medawar, 1983), The Limits of Science (1984), Memoir of a Thinking Radish (1986), married 1937 Jean Shinglewood (two sons, two daughters), died 2 October 1987.

A SALUTE TO PETER B. MEDAWAR

(by Rupert Billingham, Leslie Brent, Avrion Mitchison presented at the Symposium in honor of his 65th birthday)[a]

This Symposium was organized to celebrate Peter Medawar's 65th birthday February 28, 1980. Whilst it would have been only too easy to have made the Symposium truly representative of work currently being done in the field of experimental and clinical transplantation–a field to which Peter Medawar has made such gigantic contributions over almost four decades–we decided to limit the papers to some of those who had had the good fortune to have collaborated with him in the laboratory at one time or another. Even so, the constraints of a one-day meeting limited the choice greatly and invidiously. The selection of topics was left to the contributors and the form of the talks, which are summarized in these Proceedings thanks to the generosity of the Editor, Jerry Lawrence, was left entirely open.

Peter Medawar–together with Peter Gorer and George Snell–is rightly regarded as the man who, through his early incisive experiments on allograft rejection and his collaborative work on immunological tolerance, established the science of transplantation immunology. His influence spread far wider, however, in that it led to the era of cellular immunology. His achievements are well documented by his selected publications list and by his curriculum vitae. Our remarks are therefore not so much concerned with his scientific work as with Peter as man, colleague, and friend.

As a teacher and head of a research group Peter always led from the front, not by exhortation but by example. The joyous enthusiasm he had for experimental work was instantly communicated to those working with him, and whilst he eschewed pompousness, he had–and of course still has–a natural dignity that always commanded respect. He was disdainful of cant and all forms of woolly Naturphilosophie, and this is well illustrated by his writing, which is direct and to the point and yet studded with vivid and memorable phrases.

Simplicity was the hallmark of his experimental approach, too. He had a healthy skepticism of unduly complex experimental design and many of his most noteworthy experimental findings were made with scissors, scalpel, and syringe. Perhaps the most expensive piece of equipment he ever purchased was a high-speed centrifuge in the mid-fifties, which enabled him to make a start on the isolation and characterization of subcellular histocompatibility antigens.

It was unalloyed pleasure to work with Peter as a student or colleague. One of his characteristics that springs most readily to mind when thinking of the past is his generosity and openness of mind. He respected anyone with an original idea, regardless of who he was or where he came from, and he was always willing and eager to listen to the views of junior colleagues, whom he accepted as full partners. It was entirely in keeping with this attitude that he should have insisted that the first public communication of immunological tolerance at a meeting of the British Society for Experimental Biology in 1952 was to be made by the most junior member of the research trio. It was equally in character that he was adamant in his refusal to be a coauthor of papers to which he had not made a substantial conceptual or practical contribution, as for example in the papers published on graft-versus-host disease. He was, and is, a man of absolute integrity in all his dealings.

---

[a] Reprinted with permission of publisher (Cellular Immunology 1981, 62:241).

Though (nearly) always elegantly polite Peter has a strongly developed sense of fair play which has led him to take up the cudgels for anyone near him whom he believed to have been abused or wronged. He could be fiercely protective on behalf of nonacademic staff in his department and this led, on one occasion, to a confrontation with an equally celebrated but far more senior scientist that would have been worthy of a niche in a novel by C.P. Snow! Yet he was not easily deceived; one exception that springs to mind came about in 1953, when a farmer and his very attractive wife arrived in the department to sell him a couple of newly hatched chicks for the then, princely sum of £25. These chicks, they claimed with conviction, had been seen to emerge from the same egg, though it was discovered soon enough that they were neither chimeric for red blood cells nor tolerant of each other's skin grafts.

Perhaps we have made Peter sound too good to be true; so much brilliance must surely have been hard to live with? That was not so at all, for he has always had a well-developed and at times impish sense of humor. He was a benign father figure in those early days, who despite his deep involvement in the pursuit of science always found the time to concern himself both with the people he worked with and with the world at large. His enthusiasm for music and chess and his zestful participation in cricket and squash–those rather English games that have yet to conquer the world and no doubt will in time–were spontaneous and infectious. ("Hey, let's take the afternoon off to watch the West Indians at Lords–you've persecuted enough mice for today," or "Jenufa is on at Covent Garden, I'll see whether I can get some tickets for tonight"–and he did–were typical.) Once or twice a week there would be a departmental gathering in the local pub at the end of the day, with beer and bar billiards and a lot of scintillating and wide-ranging conversation, joined on rare occasions by MacFarlane Burnet on one of his forays into Europe. And for a few years there were the irregular but always welcome meetings with Peter Gorer, usually over a sumptuous meal out, with one or two colleagues from both "camps" joining the feast. Bernard Amos and Ted Boyse, both colleagues of Peter Gorer, will remember those occasions with as much pleasure and nostalgia as we do. They were brought to an end by Gorer's untimely death in 1961.

Peter's towering strength of character and unbending determination were tested to the limit when he was so tragically smitten by illness in 1969. With the unceasing loving support of his wife Jean he has succeeded in conquering his affliction, to the admiration of all his friends.

We salute not only Peter Medawar the brilliant scientist, but also Peter Medawar the "complete man," and we wish him and his wife Jean many more years of happy and productive work.

FOREWORD TO *THE THREAT AND THE GLORY* - A POSTHUMOUS COLLECTION OF MEDAWAR'S ESSAYS AND SPEECHES

(Lewis Thomas)[a]

Peter Medawar possessed more friends, all around the world, than anyone I have ever known or heard of. Possessed is the word; they hung on his words, read with close attention and vast pleasure everything he wrote, rejoiced in his achievements, worried endlessly about his health, wondered at his knack for survival and his outright defiance of all the rules of neurology, and adored him. Fifty, a hundred years from now, Medawar will be a steady source of PhD theses for graduate students from any number of disciplines - biology and immunology, of course, since he and his colleagues opened up the fields cleared by Ehrlich, Bordet, and Landsteiner in earlier generations, revealing in a stroke of classical Medawar experimentation the new and entrancing depths lying just below. I can already imagine the doctoral dissertations; the tolerance of mice, the tolerance of twin cows, something less than tolerance of psychoanalysis, outright immunologic rejection of Teilhard de Chardin, the acceptance and revascularization of Francis Bacon.

Then there will be the other scholars, deep in another wing of the library stacks, the Eng. Lit. graduate students on the track of Medawar the twentieth-century man of letters. His books - those still on the shelves, together with any number of proceedings of international congresses and biological symposia. These latter will, I predict, be of special interest, for Peter is in those proceedings, on the record, with some of the wisest and wittiest remarks of the twentieth century.

Something that I hope will not be missed: the electromagnetic energy of this spectacular man, his exuberance, his outrageous disrespect for so many canons of all stripes and definitions), and most important of all, his own deep pleasure in life, his immense respect for Jean, and all the fun he had all his life, with his astonishing and capacious mind.

And then, of course, there will be the philosophy students, fingering earnestly through the stacks trying to make sense of the twentieth century and discovering, I hope, through a close reading of Medawar's works, that the century made whatever sense it turned out to make because of science. This was his central conviction, the sources of his faith and pleasure, his tenacious hope for the future.

He has left intellectual marks all through the laboratories of American and European universities, and it is altogether fitting and proper to celebrate so extraordinary a life.

---

[a] Those were the words I used to honor Peter Medawar's memory at a meeting of his friends in New York soon after he died. I report them now to introduce this selection of his writings left behind, made by his friend David Pyke. It is a surprise and pleasure that there are so many. *The Threat and the Glory* will be a delight for those who know Sir Peter's writings and for those who still have that treat to come.

INTRODUCTION TO *THE THREAT AND THE GLORY*

(by David Pyke, editor)

Sir Peter Medawar was three great men. He was a great scientist, a man of great courage–and a great writer. He was supremely creative both as a scientist and as a writer, defining creativity as 'the faculty of mind or spirit that empowers us to bring into existence, ostensibly out of nothing, something of beauty, order or significance.' His creativity in literature was shown in his volumes of essays, especially in *The Art of the Soluble* and *The Hope of Progress*. They consisted largely of reviews, talks, or lectures and, though they were about science and scientists, were written for a general audience.

If I seem to labour the point by saying that he was a great writer as a scientist it is partly because I agree with him that a man's style of writing is an important part of his character–some would say one of the most revealing parts. His recipe for good writing was this: 'Brevity, cogency and clarity are the principal virtues and the greatest of these is clarity.'

Peter was born in Brazil in 1915 of a Lebanese father and English mother. He was sent to school in England and lived there for the rest of his life. When he was still at preparatory school he realized that he was 'hooked on science; no other kind of life would do.' He went to Marlborough, then Magdalen College, Oxford. He got a first class degree in Zoology and then became a Research Fellow.

After exploring various lines of research he focused on the problem of why skin is rejected when grafted from one person to another. He showed that the rejection of skin, kidney, or any other organ is under immunological control. Previously rejection had been considered genetic in origin and therefore insurmountable. But after five years' work he demonstrated, in a series of brilliant experiments, that the barrier could be overcome. The importance of the discovery, which depends upon grafting 'foreign' cells into an animal while it is still in utero, was immediately appreciated and led to the award of the Nobel Prize in 1960. It gave great encouragement to the whole medical scientific community and created the new specialty of transplant surgery. Immunologists from all over the world came to work with him and any budding transplant surgeon hoped to have the chance to do so. Peter's discovery of 'immunological tolerance' was important not because it showed *how* rejection by one person of tissue from another could be overcome but that it *could* be overcome. Today's techniques of immune suppression use complex drugs; they would not have been discovered–or not discovered as soon as they were–without Peter's work. He showed the way.

Peter had written about science and scientists for a general audience in *The Uniqueness of the Individual* in 1957 and in the BBC Reith Lectures *The Future of Man* in 1959. After the Nobel Prize in 1960 he was asked to speak, review, and broadcast all over the world. He had a great drive to convey to others the meaning and importance of science and to explain his own passion for it. Unlike most scientists he was interested in the philosophy of science, the process of scientific discovery. Science progresses by imaginative leaps which are put to the test in the laboratory: if they fail the test the ideas are discarded, if they pass they survive until late experiments refute or modify them. But what produces the ideas in the first place? They do not enter a vacant mind nor emerge from a heap of randomly assembled observations. The most interesting and exciting of all intellectual problems is how the imagination is harnessed for the performance of scientific work, so that the steam, instead of blowing off in picturesque clouds and rattling the lid of the kettle is now made to turn the wheel.

Peter was consumed by science, 'incomparably the most successful activity human beings have ever engaged upon.' It gave him no rest. Scientists are often thought of as problem-solvers. But they are more than that, they are problem-seeking creatures too. 'The motive force that is behind the scientist and technologist's almost compulsive desire for an understanding and mastery of nature is sometimes described as "curiosity" or "inquisitiveness," but these nursery words hardly do justice to what feels like a deep-seated biological impulsion–the hunting feeling, I call it myself.'

Some non-scientists, and perhaps scientists, look with alarm at the progress of science, and the enormous accumulation of facts. They fear that we shall all be overwhelmed by the sheer size of the store of information. On the contrary 'the ballast of factual information, so far from being just about to sink us, is growing daily less...In all sciences we are being progressively relieved of the burden of singular instances, the tyranny of the particular. We need no longer record the fall of every apple.'

Peter's writings became famous. One of the most famous was his devastating review of Teilhard de Chardin's *The Phenomenon of Man*. Teilhard was a French priest who claimed to have proved the existence of God scientifically and was widely acclaimed for having done so. But his style was, to put it mildly, opaque. Peter hated opacity in thought or writing. 'People who write obscurely are either unskilled in writing or up to some mischief.' Peter wrote of Teilhards' 'tipsy, euphoristic prose-poetry' which 'a feeble argument was abominably expressed'. 'It is written in an all but totally unintelligible style, and this is construed as prima facie evidence of profundity.' He saw similar pretensions and obscurity in some of the writings of psychoanalysts, whom he condemned for 'the Olympian glibness of their thought, their complete lack of hesitancy and bewilderment in the face of enormously difficulty problems. On the contrary a lava-flow of ad hoc explanations pours over and around all difficulties, leaving only a few smoothly rounded prominences to mark where they might have lain.'

Much of Peter's writing was lighthearted, but all was serious. Nowhere is this better shown than in the last lines of his review of J.D. Watson's book *The Double Helix*. Watson was the co-discoverer of the structure of DNA, the most important biological discovery of the twentieth century, which explains how characteristics are passed from one generation to the next. His book is amusing, irreverent, naive, revealing, and vulgar. 'The characters in the discovery of DNA come out larger than life, perhaps, and as different one from another as Caterpillar and Mad Hatter. Watson's childlike vision makes them seem like the creatures of a Wonderland, all at a strange contentious noisy tea party which made room for him because for people like him, at his particular kind of party, there is always room.' Those last fourteen words contain Peter's real message.

Watson was accused of excessive ambition and hunger for priority. Peter saw it differently. A scientist's discovery, unlike an artist's creation, is his only in the sense that he made it first. Peter described the difference between artistic and scientific priority in a letter declining to take part in a BBC radio game of scientist versus artists. 'Darwin's claim could not be defended against Beethoven's, even in fun...I don't think any scientist can be defended against a major artist; scientists are always dispensable, for, in the long run, others will do what they have been unable to do themselves.'

In 1962 Peter became Director of the National Institute for Medical Research at Mill Hill in London. He set himself to master the job and get to know all the 200 staff at the Institute. He administered the business in three and a half days a week and kept Tuesdays and Thursdays for his own research. Under his direction, the National

Institute became a world leader in immunology.

It was as certain as anything can be that he would have been elected President of the Royal Society. This was perhaps the one honour he ever coveted–head of his profession and heir of Isaac Newton. He was riding the crest of a very large wave. There seemed no reason why it should not go on and on.

The wave broke on Sunday, 6 September 1969. Peter, as president, was reading the lesson in Exeter Cathedral at the annual service of the British Association for the Advancement of Science when his voice started to falter. He was helped back to his seat and there sank into unconsciousness. He had had a large cerebral hemorrhage. He was in the hospital for months and was near to death twice. While still very ill and when no one knew how badly his mind had been affected he joked about his reading of the lesson in Exeter Cathedral: 'People simply don't know the risks they run when they meddle with the supernatural.' He knew how ill he had been: his reaction was characteristic: 'I myself, naturally sanguine, had considered and dismissed the possibility of dying.'

His experiences in hospital and his close encounters with death did not cause him to bother about the 'dignity' of dying. As he wrote years later: 'No thought of dignity entered my head - it is a state of mind not easily compatible with the hospital microcosm of bedpans and catheters. I needed all the help I could get to promote my ambition to remain alive. It was as allies, then, that I regarded my physicians and the apparatus of intensive care and not as so many plots to deprive me of my dignity.'

His sanguine attitude to life put him out of sympathy with people such as Ivan Illich and Thomas McKeown who ascribe all improvements in health over the last century to social and economic factors and dismiss the advances of clinical medicine. 'So long as human beings retain their strong preference for being alive as opposed to being dead so long will medical treatment, if necessary of a strenuous and heroic character, remain in demand. I myself should rather not have needed treatment, but as I did need it, thank God I got it.' Peter got the treatment all right but for the rest of his life he was paralysed in the left arm and leg and could not see anything on the left side of his visual field.

He went back to work in 1970, although not with quite the same ferocious intensity as before. He could not use his left hand, so he could no longer do animal experiments. He started to travel again, always with his wife Jean who, as he put it, was his third leg and arm and eye. His enormous scientific output fell after 1969, but his literary output did not. He wrote seven books (not counting *The Hope of Progress*, published in 1972 but consisting of essays written before 1969). He also gave lectures and radio talks and wrote many reviews.

In 1980, while in New York, Peter had another stroke in the mid-brain which affected speech, swallowing, and walking. Again there was gradual recovery but it was not complete. He went on working, writing, speaking, and travelling; supported by Jean, making little of his difficulties.

What a figure he was - 6'4", still extremely handsome, half blind, walking with a stick and caliper, his left arm in a sling, his speech a little indistinct but punctuated by laughter. His physical problems were ignored. He was 'heroic in his indifference to increasing disability.' Nothing seemed to impair his enjoyment of life. His enjoyment was infectious. He loved to have company, and he was far more sociable than he had been before 1969 when he could seem austere and formidable. His friends loved to be with him. There was none of the reluctance or embarrassment one sometimes feels on being with an old friend who is so afflicted; he accepted the situation as it was and as he knew it would remain - until it got worse. It did get worse, in June 1985, a few days after he had finished his autobiographical *Memoir of a Thinking Radish.* He had several more strokes until at last, on 2 October 1987, at the age of seventy-two, he died.

When Peter had his third stroke in 1985 there were still many articles and reviews which had not been published in book form. Oxford University Press asked him that year to make a selection for a new book, but by this time he could no longer manage it. It has been an honour to be asked to prepare this book for publication and a labour of love to write this introduction. In doing so, I can say, as Peter did in the introduction to *The Hope of Progress*, that Jean Medawar's help and encouragement have been decisive.

Many of the essays reprinted here have not previously been published in book form. Most are book reviews; I have chosen them from papers Peter left at his death, because they are of general interest and because they do not duplicate others in this or any previous volumes. All but five were written after his first stroke, eight after his second, when he was half paralyzed and half blind. Two exceptions are broadcasts, 'My Life in Science' (Chapter 1), not previously published, and 'Is the Scientific Paper a Fraud?' (Chapter 15), a famous talk which appeared in *The Listener* in 1963. The other three have been published in previous books but are now out of print. 'The Genetic Improvement of Man,' a paper in honour of his co-Nobel Laureate MacFarlane Burnet, was to have been given by Peter in Australia in September 1969 but had to be read for him; 'Animal Experimentation in a Medical Research Institute,' written from his experience at the National Institute for Medical Research at Mill Hill, is at least as topical and important today as when it was written. Both of these were published in *The Hope of Progress* (Methuen, 1972). 'The Future of Man' comprises the 1959 BBC Reith Lectures. As Peter himself agreed they are tightly argued and therefore solid going, but they are written with his characteristic intensity of purpose, clarity of style, and lightness of touch. After thirty years they are still well worth reading.

I had the great good fortune to know Peter well. We first met in 1959 when his wife Jean joined me in editing a journal on family planning. After his stroke in 1969 when he spent more time at home I came to know him better and to admire him even more. I was once asked if I thought his stroke had affected his intelligence. I said I thought it had: it had reduced his IQ to three figures.

I want to end with Peter's description of the qualities needed by a scientist: 'A sanguine temperament that expects to be able to solve a problem; power of application and that kind of fortitude that keeps them erect in the face of much that might otherwise cast them down; and above all, persistence, a refusal bordering upon obstinacy to give up and admit defeat.'

Peter Medawar wrote that about scientists. It could have been written about himself.

CURRICULUM VITAE

Peter Brian Medawar

February 28, 1915 - October 2, 1987

PERSONAL

Born: Rio de Janeiro

EDUCATION

1928-32	Marlborough College
1932-35	Magdalen College, Oxford
1938-47	Fellow
1961	Honorary Fellow

POSITIONS

1938-47	Lecturer in Zoology Department University of Oxford
1947-51	Mason Professor of Zoology University of Birmingham
1951-62	Jodrell Professor of Zoology University College, London
1962-71	Director, National Institute for Medical Research London (Medical Research Council)
1971-	MRC External Staff at Clinical Research Center, Northwick Park Harrow, Middlesex

DEGREES

M.A., D.Sc. (Oxon)

Honorary Doctor of the Universities of Alberta, Aston, Birmingham, Brazil, British Columbia, Brussels, Cambridge, Chicago, Dalhousie, Dundee, Exeter, Glasgow, Hull, Liège, London, Southampton, South Florida, Washington, Seattle, Washington University, St. Louis

Honorary Fellow of Magdalen College and of St. Catharine's College, Oxford; Honorary Fellow of University College, London

LECTURESHIPS

Croonian Lecture (Royal Society)
Dunham Lectures (Harvard)
Harvey Lecture (New York)
Herbert Spencer Lecture (Oxford)
Jayne Lectures (American Philosophical Society)
Prather Lectures (Harvard)
Reith Lectures (British Broadcasting Corporation)
Romanes Lecture (Oxford)
Withering Lectures (Birmingham University)

ACADEMIC HONORS

1949	FRS
1959	Royal Medal of Royal Society
1960	Nobel Prize in Physiology or Medicine
1967	Society of Apothecaries Gold Medal in Therapeutics
1969	Copley Medal of the Royal Society

CIVIL HONOURS

1958	CBE
1965	Knight Bachelor
1972	Companion of Honour
1981	Order of Merit

HONORARY AFFILIATIONS

National Academy of Sciences, USA
American Philosophical Society
American Academy of Arts and Sciences
New York Academy of Sciences
American College of Physicians
Royal Canadian College of Physicians and Surgeons
Royal Belgian Academy of Medicine
Indian Academy of Sciences
Royal Society of Edinburgh
Royal College of Surgeons
Royal College of Physicians
Royal Society of Medicine
Royal College of Pathologists
Professor of Experimental Medicine, The Royal Institution

BOOKS

1956	The Uniqueness of the Individual
1960	The Future of Man
1967	The Art of the Soluble
1969	Induction and Intuition in Scientific Thought
1972	The Hope of Progress
1977	The Life Science (with J.S. Medawar)
1979	Advice to a Young Scientist
1982	Pluto's Republic
1983	Aristotle to Zoos
1984	The Limits of Science
1986	Memoir of a Thinking Radish

1984	The Limits of Science
1986	Memoir of a Thinking Radish
1990	The Power and the Glory

FORMER STUDENTS AND RESEARCH COLLEAGUES

T. Gibson
Doug Darcy
Ruth Clayton
G.H. Lampkin
Rupert Billingham
Elizabeth Cobb (nee Sparrow)
June Merchant
Thelma Boswell
Av Mitchison
Peter Krohn
Leslie Brent
Paul Russell
George Szabo
Bill Hildemann
Paul Terasaki
John Dineen
Jean Deinhard (nee Brown)
Marian Ruszkiewicz
Michael Edidin
Gene Lance
Ray Levey
Jerry Lawrence
Bob Taub
Liz Simpson
Sandra Nehlsen
Rosemary Marchant (nee Birbeck)
Jean Morris (nee Gardner)
George Floersheim
John Castro
Jurgen Mertin
Chris Mead
Ruth Hunt
Don Pinto
David Hamilton

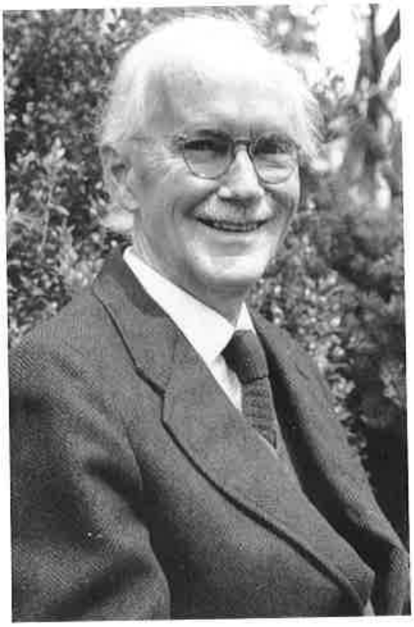
A GENETICIST'S RECOLLECTIONS OF EARLY TRANSPLANTATION STUDIES

George D. Snell

Address: 21 Atlantic Avenue
Bar Harbor, Maine 04609

George D. Snell

ca. 1953



1981

1990

A GENETICIST'S RECOLLECTIONS OF EARLY TRANSPLANTATION STUDIES

George D. Snell

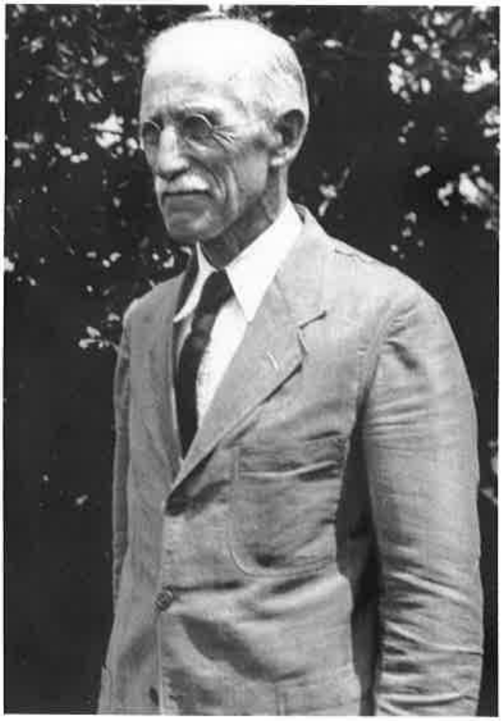
Because I retired from active research in 1973 at age 70, and because my personal contact with transplantation research goes back to the earliest years of work in this area, my contribution to this *History of Transplantation* will emphasize these early years. Also, because for a considerable period I was, with the exception of Peter Gorer in England, the only person concentrating on studies of transplantation genetics, parts of this review will be quite personal.

Clarence Cook Little, more than any other person, pioneered studies in transplantation genetics. A graduate of Harvard, Little did his graduate work with Dr. William Castle, the father of mammalian genetics in this country. After serving for brief periods as President of the University of Maine and the University of Michigan, he decided that his true love was mammalian genetics. This led to the founding, in 1929, of the Jackson Laboratory in Bar Harbor, Maine.

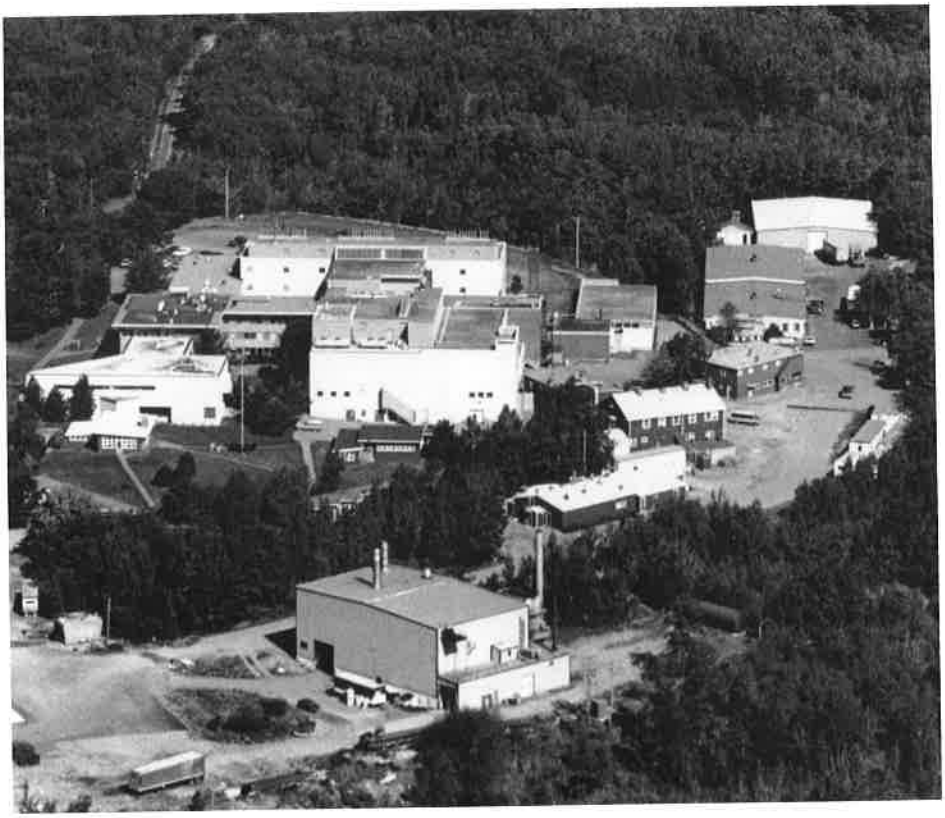
Like Little, who was 18 years my senior, I was brought up in Brookline, Massachusetts and did my graduate work with Dr. Castle. Both of us had concentrated on mouse genetics. When, after a year of teaching, I decided, as Little had done, that my real bent was mammalian genetics, it was inevitable that I apply for a job at the one place where this sort of work was being done, the Jackson Laboratory.

That was in 1935. The status of the laboratory at that time is illustrated by an experience on my arrival in Bar Harbor in my model A Ford roadster. I stopped at a garage and asked the location of the Jackson Laboratory. The man I spoke to hesitated a moment and then replied, "Oh, you mean the mouse house." The total staff at that time consisted of seven people, and it was the departure of one of them that left an opening for me. There were also seven young men who took care of the mice and washed the mouse boxes. The laboratory, by way of comparison, now has over 500 employees.

The original work at the laboratory had been on the genetics of transplantation, but because this work was terminated prior to my arrival, I did not learn of it until some time later. Only Arthur Cloudman, who kept a number of transplantable tumors going,



William E. Castle, 1929, the founding father of mammalian genetics in the United States.



The Jackson Laboratory.

Nathan Kaliss

Peter Gorer

had any involvement in transplantation when I joined the staff. My own early work at the laboratory was a genetic analysis of some reciprocal translocations in mice which I had induced with x-rays during two years as a postdoctoral fellow at the University of Texas. It was because I took on the job of editing *The Biology of the Laboratory Mouse* in 1938, and in the process necessarily read Dr. Little's chapter, "The Genetics of Tumor Transplantation" (1), that I learned of this early work.

What these early studies had shown was that the resistance to tumors transplanted into foreign strains of mice was determined by multiple genes. It seemed to me, on learning of this work, that it would be a matter of considerable interest if it were possible to identify some of the individual genes. The first thing I needed was a name for the genes and, at the suggestion of Bill Russell, my neighbor across the hall, I adopted the name "histocompatibility" genes or H genes.

It seemed to me that there were two possible approaches to the problem of identifying these genes. The first was to look for H genes linked to known and easily recognized marker genes. The second was a much more time-consuming but potentially very powerful method - the production of congenic resistant (CR) lines (2). These lines were, by definition, lines that differed from a standard inbred strain by a single histocompatibility gene. Such lines could be produced by the introduction of a foreign H gene (and, of necessity, closely linked genes) into an inbred strain by an appropriate series of crosses, accompanied by repeated tests to determine the presence or absence of the gene in question.

I was lucky in the linkage tests. The very first cross I used turned up a linkage between Fu, or fused tail, and a strong histocompatibility locus, subsequently given the designation H-2 (3). Over the years, H-2 actually has been shown to be a whole complex of genes (4).

In 1948 I set up the meetings for the production of congenic-resistant strains. One hundred twenty-five lines were started, but many were lost in the production process. Only 27 lines were carried through to completion, and 22 of these turned out to have differences at H-2. Between the linkage method and the CR method, a number of non-H-2 histocompatibility loci was discovered, of which H-3 and H-4 have turned out to be the most interesting (5-7). These CR strains and others produced by other investigators, especially Jack Stimpfling, have been widely used.

An area of research in which I was briefly involved before I decided to concentrate on histocompatibility genes was immunological enhancement. It had been known for some time that a mouse in which a tumor from a foreign strain had grown and then regressed showed virtually no growth of a second transplant of the same tumor. I thought it would be interesting to see if this tumor immunity could be induced with freeze-dried tumor tissue. The relevant tests were set up in 1946-1947 jointly with Cloudman and Failor (8). Much to our surprise, the injected mice, instead of showing inhibition, grew the tumor progressively. Nathan Kaliss, who joined the staff in 1947, continued these studies, and jointly with Molomut (9) showed that antiserum against the donor strains could produce enhancement. It was years before we fully understood this phenomenon, but, briefly stated, it depends on the fact that there are two kinds of immunity; humoral and cellular. Graft rejection is typically due to the cellular variety, which is mediated by immune lymphocytes. In a mouse with humoral or antibody-mediated immunity, the formation of cellular immunity is blocked. Since killed tissues induce humoral, not cellular, immunity, they block the subsequent induction of cellular immunity by living tissues (10).

So much for my own early research. Over the years, more and more people became involved in histocompatibility studies, some of them at the Jackson Laboratory but increasingly at other laboratories.

One other lone pioneer, and a very important one, was Peter Gorer, whose early work substantially antedated mine. His approach was serological - the identification of antigenic differences between strains. His classic paper, "The Genetic and Antigenic Basis of Tumor Transplantation," was published in 1937 (11), but because Little, in his chapter in *The Biology of the Laboratory Mouse*, made no mention of Gorer's work, I did not learn of it until Gorer came to the laboratory in 1946 for a year of cooperative research. The main outcome of this joint study was the demonstration that the locus that Gorer had identified serologically and the locus that I had identified by linkage studies were one and the same, the locus designated H-2 (3).

Over a 25-year period, Gorer was author or coauthor of numerous papers. Also, as we shall see, his serological approach to transplantation antigens was picked up by other investigators and became a mainstay of transplantation research. So important was this area that had it not been for Gorer's untimely death he might very well have won a Nobel Prize.

Peter Gorer (left) with Sir Peter Medawar.

A major area of research in this early period was skin transplantation studies. Billingham, Brent, and Medawar were the pioneers in this area (12). The original report of a technique of skin grafting in rabbits was published by Medawar in 1944 (13). Probably the most important finding, made in a joint study, was that a graft of foreign skin made to an unborn mouse would survive. This led to the concept of immunological tolerance. Perhaps I under-

Jean Dausset (left) with Baruj Benacerraf

Baruj Benacerraf

Dr. Billingham in 1979

Ian McKenzie

Drs. Billingham (left) and Brent

appreciated this work, but later events altered this early judgment.

Beginning in about 1952 to 1953, there was a considerable expansion in studies of histocompatibility genetics. An event I remember with considerable pleasure was a Tissue Transplantation Conference organized by E. J. Eichwald and held October 7 and 8, 1952 at the old Harriman mansion in the upper Hudson River area of New York state. It was in 1952, also, that Kaliss and Molomut reported, as already mentioned, the survival of tumor homografts on mice injected with antiserum to mouse tissue. In September 1953, the first issue of *Transplantation Bulletin* was published. Eichwald was the editor. It was about this time also that a series of studies by Jean Dausset in Paris led to the recognition of HLA, the human homolog of H-2. Somewhat later, Van Rood in Holland became a major contributor to HLA research (14).

The linkage of Fu with H-2 could be used to identify new H-2 alleles, and I devoted considerable effort to the use of this method. In 1951, Snell and Higgins reported the existence of four H-2 alleles, and by 1953 I had brought this up to seven (15,16). Subsequently, the number was increased greatly by several investigators using Gorer's serological technique (17-20).

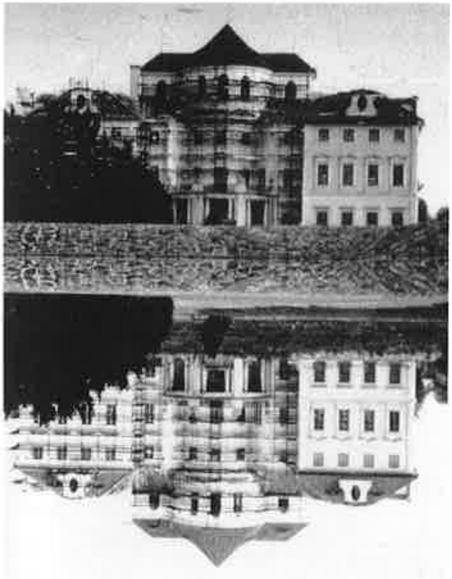
It was also shown subsequently that this complexity was the result of H-2 being a group of closely-linked loci rather than a single locus (4).

About this time my interest shifted from H-2 to non-H-2 research. My first report on this new area, published jointly with Diane Kelton in 1953, was "H-1, a New First Chromosome Locus in the Mouse Determining Susceptibility and Resistance to Tumor Transplants" (21). If I remember correctly, I had already reported preliminary evidence for H-3 and H-4 at the Harriman conference. It was in 1953 again that Bernard Amos, a student of Gorer's currently at Duke University who has used Gorer's immunological approach, published his first paper (22). Gustavo Hoecker, working at the Jackson Laboratory in collaboration with Shiela Counce and Priscilla Smith and also using Gorer's immunological methods, fur-

Back row (L-R): Donald Shreffler, Bernard Amos, Gustavo Hoecker;
Front row (L-R): Rhoda Snell, George Snell, Elizabeth Goru, Henry Winn.

Donald Bailey

Ben Taylor



Liblice, an old mansion some miles from Prague, Czechoslovakia, where several delightful H-2 meetings were held.

Alena Lengerova organized H-2 meetings at Liblice.

Derry Roopinean

Peter Demant

Jan Klein

(Left to right) Igor Egorov, Mrs. Snell, George Snell.

ther demonstrated the antigenic complexity of H-2 in 1954 (23). In the same year, Avrion Mitchison showed that immunity to grafts could be transferred with lymphocytes of immune mice (24). And in 1955, Eichwald and Silmser reported the discovery of a gene on the Y chromosome that caused the rejection of male-to-female grafts (25).

As time went on, more and more laboratories took up the study of H-2, and the result was a growing recognition of the complexity of the chromosome region which it occupies and of its importance in immune reactions. Some early work with which I was involved had hinted at this complexity. In a joint study with Cloudman and Failor, it was shown that some strain-A tumors would grow in hybrids between strain DBA/2 and a strain called K (26). It was Gorer who suggested the correct explanation - that two loci were involved (27). DBA/2 possessed the strain A allele at one of the loci and strain K the strain A allele at the other. This was the original evidence of the D and K regions of the H-2 complex.

Proof that H-2 is divisible required crossover studies. In a 1955 test of the linkage of H-2 and Fu, Allen obtained evidence of a crossover within H-2 (28). Gorer and Mikulska, in a specific search for crossovers, found several (29). Stimpfling subsequently took up the study, and while confirming the occurrence of crossovers, showed that the frequency is quite low (30). The crossover stocks resulting from these studies have been a major source of information concerning the complexity of H-2.

In 1962, Shreffler documented another complexity by demonstrating an H-2-linked locus, Ss, responsible for determining two forms of a serum protein (31). And in 1968, McDevitt found an H-2-linked locus that influences the immune response to various antigens, including transplantation antigens. Benacerraf at Harvard made the same discovery independently (32). In 1962, Davies in England reported some work on H-2 chemistry, and in the late 1960s, Nathenson began studies that were to lead to a substantial understanding of the chemistry of the various H-2 region products (33,34). In 1974, Zinkernagel reported the phenomenon of H-2 restriction in the cytotoxicity of T-effector cells immunized against non-H-2 cell surface antigens. Cytotoxicity was manifest only when the effector cells and the target cells shared the same H-2 type (35).

While it was apparent right from the beginning that H-2 played a special role in transplantation phenomena, a 1956 study by Counce, Smith, Barth, and I made this specific. Donor-recipient strain pairs with an H-2 difference were better able to survive tumor transplants and showed more rapid rejection of skin grafts than did donor-recipient pairs with an H-1 or an H-3 difference (36). Ralph Graff, Bill Hildemann, and I, working at the Jackson Laboratory, extended this finding (37). It was when Donald Bailey joined the laboratory staff in 1966 that I really saw the study of H genes blossom. Bailey developed an ingenious and rapid method of tail skin grafting. He also produced the first recombinant inbred strain, and many more were added by Ben Taylor (38,39). These strains have become a major tool in the mapping of mouse genes. Forty-eight murine H gene loci have been identified of which 37 have been located on the chromosome map. This actually is an understatement since Derry Roopenian at the Jackson Laboratory has shown that H-3 and H-4 can be subdivided (40-42).

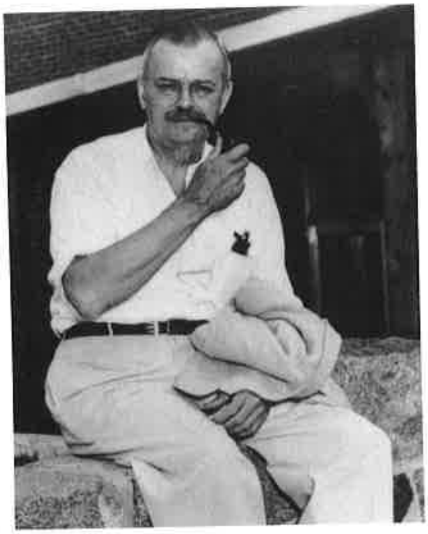
Any account of transplantation studies during my active years would be incomplete without mention of the work going on in Prague, Czechoslovakia. The group was founded by Milan Hasek and H-2 was its area of research. I first visited Czechoslovakia in 1967 at Hasek's invitation and later attended several delightful meetings there organized by Alena Lengerova and held at Liblice, an old estate some distance outside Prague. Two members of Hasek's group each spent a year at the Jackson Laboratory, Ivan Hilgert in 1966-67 and Peter Demant in 1968-69. This was a period when Czechoslovakia was blessed with a relatively liberal government. A number of years later, after the government had become more repressive, all 17 members of the Prague group were fortunate in being able to escape, and all of them are now located in European laboratories. It has been my good fortune to maintain contact with Peter Demant and another member of the group, Jan Klein, both very dear friends.

Another refugee from a communist country, Russia, was Igor Egorov. Igor and his wife, Olga, fled Russia somewhat prior to 1980 but spent their first years with Amos in South Carolina. In 1980, the Egorovs moved to Bar Harbor and joined the laboratory staff. Igor's area of interest has been mutations at the H-2 locus, and I had corresponded with him about this work when he was still in Russia (43).

The last area of research in which I was involved, jointly with Marianna Cherry and Ian McKenzie, was the identification of alloantigens on lymphocytes by means of the chromium-labelled cytotoxic test (44). This technique was pioneered in England by Davies and others (45). One of the first findings based on a cytotoxic technique was the discovery by Reif of the Thy-1 antigen. Thy-1 is notable for its odd distribution: It occurs on thymocytes and in the brain (46).

Of course surgeons were experimenting with skin and organ transplantation through most of my career, and although I was aware of this work, I was totally uninvolved.

In June 1987, a meeting organized by Chela David and Henry Winn was held at the Jackson Laboratory celebrating the 50th anniversary of the discovery of H-2. It drew a large attendance. It was a happy closing event to look back on as I write these recollections of transplantation research (4).



S.F. Shull

Jan Klein (left) and Chella David

George Snell (left) and Peter Demant

(Left to right) Marianna Cherry, Peter Demant, and George Snell

Pavol Ivanzi (left) and Donald Bailey

REFERENCES

1. Little CC. The genetics of tumor transplantation. In: Snell GD, Ed. Biology of the Laboratory Mouse. Blakiston, Philadelphia 1941.
2. Snell GD. Methods for the study of histocompatibility genes. Genetics 1948; 49:87.
3. Gorer PA, Lyman S, Snell GD. Studies on the genetic and antigenetic basis of tumor transplantation. Linkage between a histocompatibility gene and "fused" in mice. Proc R Soc B 1948; 135:499.
4. David CS. H-2 antigens. In: David CS, Ed. Genes, Molecules, Function. Plenum Press, New York, 1987.
5. Snell GD, Kelton DE. H-1, a new first chromosome locus in the mouse, determining susceptibility and resistance to tumor transplants. Proc Am Assoc Cancer Res 1953; 1:53.
6. Snell GD, Counce S, Smith P, et al. H-3, a fifth chromosome histocompatibility locus identified in the mouse by tumor transplantation. Proc Am Assoc Cancer Res 1955; 2:47.
7. Snell GD, Stevens LC. Histocompatibility genes of mice. III. H-1 and H-4, two histocompatibility loci in the first linkage group. Immunology 1961; 4:366.
8. Snell GD, Cloudman AM, Failor E, Douglas P. Inhibition and stimulation of tumor histocompatibility loci in the first linkage group. J Natl Cancer Inst 1946; 6:303.
9. Kaliss N, Molomut N. The effect of prior injections of tissue antiserums on the survival of cancer homoiografts in mice. Cancer Res 1952; 12:379.
10. Snell GD, Dausset J, Nathenson S. Histocompatibility 1976; chap.13.
11. Gorer PA. The genetic and antigenic basis of tumor transplantation. J Pathol Bacteriol 1937; 44:691.
12. Billingham RE, Brent I, Medawar PB. Quantitative studies on tissue transplantation immunity. I. The survival times of skin homografts exchanged between different inbred strains of mice. Proc R Soc B 1954; 143:43.
13. Medawar PB. The behavior and fate of skin autografts and skin homografts in rabbits. J Anat 1944; 78:176.
14. van Rood JJ, van Leeuwen A. The HLA story as seen from Leiden. In: Terasaki PI, Ed. History of HLA: Ten Recollections. UCLA Tissue Typing Laboratory, Los Angeles, 1990; 33.
15. Snell GD, Higgins GF. Alleles at the histocompatibility-2 locus of the mouse as determined by tumor transplantation. Genetics 1951; 36:306.
16. Snell, GD. The genetics of transplantation. J Natl Cancer Inst 1953; 14:691.
17. Gorer PA, Mikulska ZB. The antibody response to tumor inoculation. Improved methods of antibody detection. Cancer Res 1954; 14:651.
18. Hoecker G, Pizarro O, Ramos A. Some new antigens and histocompatibility factors in the mouse. Transplant Bull 1959; 6:407.
19. Snell GD, Demant P, Cherry M. Hemagglutination and cytotoxic studies of H-2. V. The anti-27, 28, 29 family of antibodies. Folia Biol (Praha) 1974; 20:145.
20. Klein J. Biology of the Mouse Histocompatibility-2 Complex. Springer-Verlag, New York, Heidelberg, Berlin, 1973.
21. Snell GD, Kelton DE. H-1, a new first chromosome locus in the mouse, determining susceptibility and resistance to tumor transplants. Proc Am Assoc Cancer Res 1953; 1:53.
22. Amos DB. The agglutination of mouse leukocytes by iso-immune sera. Br J Exp Pathol 1953; 34:464.
23. Hoecker G, Counce S, Smith P. The antigens determined by the H-2 locus: A rhesus-like system in the mouse. Proc Natl Acad Sci USA 1954; 49:1040.

24. Mitchison NA. Passive transfer of transplantation immunity. Proc R Soc B 1954; 142:72.

25. Eichwald EJ, Silmser CR. Note without title. Tranplant Bull 1955; 2:148.

26. Snell GD. A fifth allele at the histocompatibility-2 locus of the mouse as determined by tumor transplantation. J Natl Cancer Inst 1951; 11:1299.

27. Amos DB. HLA - A mouser's recollections. In: Terasaki PI, Ed. History of HLA: Ten Recollections. UCLA Tissue Typing Laboratory, Los Angeles, 1990; 61.

28. Allen SL. Linkage relations of the genes histocompatibility-2 and fused tail, brachyury and kinky tail in the mouse, as determined by tumor transplantation. Genetics 1955; 40:627.

29. Gorer PA, Mikulska ZB. Some further data on the H-2 system of antigens. Proc R Soc B 1959; 151:57.

30. Stimpfling JH, Richardson A. Recombination within the histocompatibility-2 locus of the mouse. Genetics 1965; 51:831.

31. Shreffler DC. The Ss system of the mouse - a quantitative serum protein difference genetically controlled by the H-2 region. In: Palm J, Ed. Isoantigens and Cell Interactions. Wistar Institute Press, Philadelphia, 1965; 11.

32. McDevitt HO, Benacerraf B. Genetic control of specific immune responses. Adv Immunol 1969; 11:31.

33. Davies DAL. Clinical nature of mouse histocompatibility antigens. Nature 1962; 193:34.

34. Nathenson SG, Davies DAL. Solubilization and partial purification of mouse histocompatibility antigens from a membranous lipoprotein fraction. Proc Natl Acad Sci 1966; 56:476.

35. Zinkernagel RM, Doherty PC. Restriction of *in vitro* T-cell-mediated cytotoxicity in lymphocytic chorio-meningitis within a syngeneic or semi-allogeneic system. Nature 1974; 248:701.

36. Counce S, Smith P, Barth R, et al. Strong and weak histocompatibility gene differences in mice and their role in the rejection of homografts of tumors and skin. Ann Surgery 1956; 144:198.

37. Graff RJ, Hildemann WH, Snell GD. Histocompatibility genes of mice. VI. Allografts of mice congeneic at various non-H-2 histocompatibility loci. Transplantation 1966; 4:425.

38. Bailey DW. Recombinant-inbred strains. An aid to finding identity, linkage, and function of histocompatibility and other genes. Transplantation 1971; 11:325.

39. Taylor B. Recombinant inbred strains: Use in gene mapping. In: Morse HC, Ed., Origins of inbred mice, Academic Press, New York, 1978; 423.

40. Roopenian DC, Davis AP. Responses against antigens encoded by the H-3 histocompatibility locus: Antigens stimulating class I MHC- and class II MHC-restricted T cells are encoded by separate genes. Immunogenetics 1989; 30:335.

41. Davis AP, Roopenian DC. Complexity at the mouse minor histocompatibility locus H-4. Immunogenetics 1990; 31:7.

42. Graff RJ, Martin-Morgan D, Kurtz ME. Multiplicity of chromosome 2 histocompatibility genes: new loci, H-44 and H-45. Immunogenetics 1987; 26:111.

43. Egorov IK, Blandova ZK. Histocompatibility mutations in mice: chemical induction and linkage with the H-2 locus. Genet Res 1972; 19:133.

44. Cherry M, Snell GD. A description of a non-H-2 alloantigen in C3H/Sn mice. Transplantation 1969; 8:319.

45. Davies DAL, Hutchison AM. The serological demonstration of histocompatibility activity. Br J Exp Pathol 1961; 42:587.

46. Reif AE, Allen JM. The AKR thymic antigen and its distribution in leukemias and nervous tissues. J Exp Med 1964; 120:413.

CURRICULUM VITAE

George D. Snell

PERSONAL

Born:	December 19, 1903; Bradford, Massachusetts

EDUCATION

1926	Dartmouth College, B.S.
1930	Harvard University, Sc.D.
1967	Charles University, Prague, M.D. (Honorary)
1974	Dartmouth College, Sc.D. (Honorary)
1981	University of Maine, Sc.D. (Honorary)
1981	Gustavus Adolphus College, Sc.D. (Honorary)
1982	Colby College, LLD (Honorary)
1982	Bates College, Sc.D. (Honorary)
1984	Ohio State University, Sc.D. (Honorary)

POSITIONS

1929-30	Dartmouth College, Instructor
1930-31	Brown University, Instructor
1931-33	University of Texas, National Research Council Fellow
1933-34	Washington University, Assistant Professor
1935-57	The Jackson Laboratory, Research Associate
1949-50	Staff Scientific Director
1953-54	University of Texas, Guggenheim Fellow
1957-68	Senior Staff Scientist
1958-62	Member, NIH Allergy and Immunology Study Section
1968-73	Senior Staff Scientist, Emeritus
1973	Retired

AWARDS

1952	American Academy of Arts and Sciences
1955	Hekteon Silver Medal of the American Medical Association (Co-recipient)
1962	Griffin Award, Animal Care Panel
1962	12th Annual Bertner Foundation Award
1967	Gregor Mendel Medal, Czechoslovak Academy of Sciences
1970	National Academy of Sciences
1976	Gairdner Foundation Award
1978	National Institute of Arthritis and Infectious Disease, National Cancer Institute, Award
1978	British Transplantation Society, Honorary Member

1978	Wolf Prize in Medicine
1979	French Academy of Science, Foreign Associate
1980	Nobel Prize in Physiology or Medicine, Co-recipient with Dausset and Benacerraf
1982	American Philosophical Society
1983	British Society of Immunology, Honorary member

EDITORSHIPS AND EDITORIAL BOARDS

Biology of the Laboratory Mouse

Histocompatibility

Search for a Rational Ethic

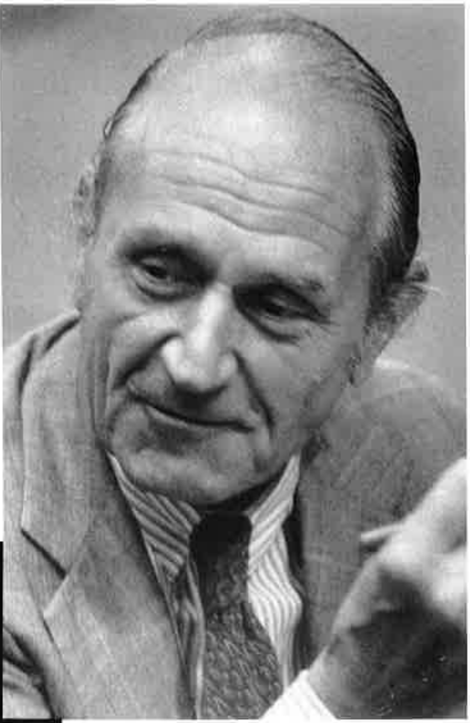
HUMAN RENAL TRANSPLANTATION MEMORIES, 1951 TO 1981

René Küss

Address: Hôpital de la Pitié
Clinique Urologie
83 Bd. de l'Hôpital
75651, Paris Cedex 13, France

1950

René Küss



1975

1980

HUMAN RENAL TRANSPLANTATION MEMORIES, 1951 TO 1981

René Küss

"Wild" Grafts

I first approached renal transplantation from my experience of experimental surgery of the urinary tract. However, in the years 1945 to 1950, the recently developed techniques of vascular surgery were not amongst the attributes of a urologist. I acquired these techniques because of the responsibility conferred to renal artery disease in the origin of certain forms of hypertension and also because of my conviction that every surgeon, even those specialized in a particular domain, should be able to apply these techniques to his own field.

During these years, we were a handful of surgeons in Paris: (J. Oudot, N. Oeconomos, J. Auvert) interested in renal transplantation in the dog, in the pelvic position with vascular anastomosis either by means of a tube or by direct anastomosis. The results of this experimentation only confirmed those obtained by Carrel at the beginning of the century, followed soon after by Williamson: the success of autologous transplants and the failure of homologous transplants.

It was only after the bombshell launched by the publication by R. Lawler from Chicago of a transplantation performed in June 1950 in a female uremic patient in the place of a polycystic kidney, that in January 1951 (without waiting for the results of this case) together with my friend J. Teinturier, we decided to progress from animal to man (1). At that time, I was assistant to Bernard Fey at the Urology Department of Hopital Cochin. Two other Parisian teams were attempting the same adventure at the same time: those led by Dubost and Oeconomos, and by Servelle and Rougeulle, when the latter was working for me. Three transplantations were performed by our three teams during the month of January. Personally, I added four others the same year.

The recipients had all reached end-stage renal failure due to a variety of medical and surgical causes (with a blood urea level ranging between 2 and 3.50 g). At this time, the prognosis of uremia was defined almost mathematically by Widal's laws: A figure exceeding 2 g was equivalent to a death sentence over the following weeks or months.

The kidneys were taken either from cadavers or from living subjects. In actual fact, the cadaver kidneys were obtained from prisoners sentenced to death who had agreed upon postmortem donation, and their kidneys were removed during the minutes following decapitation.

This use for renal transplantation of a convict's body sentenced to death had already been envisaged in Paris in the mid-1920s by Serge Voronoff (particularly interested in testicular grafts), but although he obtained the prisoner's consent, the state prosecutor refused to give his approval for this project.

I'm sure I don't need to describe such a dramatic situation and the extremely precarious conditions of these donor nephrectomies which strongly offended the sensitivity of some of us. However, despite the discomfort of the "operation," performed on the ground by torchlight, these kidneys were removed with great care and most of them were washed and perfused with Ringer's solution during transport in boxes especially designed for this purpose.

The donor nephrectomies which we performed on living subjects were carried out in our urological departments on ABO-compatible subjects. Removal of the kidney was justified for therapeutic reasons: a limited lesion of the parenchyma or a lesion in the excretory tract (tuberculosis, renal stones, uretohydronephrosis). These kidneys were removed in an operating room adjacent to the room in which they were subsequently transplanted. These transplantations from living donors done in 1951, were perhaps the first to be performed in the history of renal transplantation (1).

We used an original transplantation technique. The kidneys were transplanted via a retroperitoneal approach in the contralateral iliopelvic region. The left kidney was preferred because of the length of its vein...in some cases the kidney was tossed when two teams shared the kidneys from the same cadaver! The renal pedicle was anastomosed to the iliac vessels, the renal vein was anastomosed end-to-end with the external iliac vein with an essentially identical caliber, and the renal artery was anastomosed end-to-end to the hypogastric artery. I selected the hypogastric artery because its size was, at its origin, always greater than that of the renal artery and its cylindro-conical shape, depending on the level of section, always provided a caliber corresponding to that of the renal artery with a blood flow rate very close to normal. The ureter was sutured to the skin in order to monitor graft function.

These transplanted kidneys (one died from intraoperative cardiac arrest) (1) excreted between 20 cm^3 and 350 cm^3 of urine, but only very transiently. These attempts at homologous transplantation all resulted in failures with death of a patient in the days or weeks following the operation; they confirmed the findings of animal experimentation and the few cases reported in man.

At this time, like our distant predecessors, we attributed the failure of these transplantations to "biological incompatibility between the donor and the recipient, the intransigence of individual specificity which results in the rejection of any foreign tissue, and concluded that "in the present state of knowledge, the only rational transplantation would be an exchange between monozygotic twins" (2).

This very situation arose three years later in 1954 with a successful result in the hands of Murray, Merrill, and Harrison at Brigham Hospital which subsequently became the Mecca of renal transplantation. In retrospect, we believe that our failures were largely due to factors other than incompatibility: quality of the graft, ischemia time, unsatisfactory vascular anastomoses due to frequently encountered vascular anomalies, very precarious intensive care techniques at the time in the preparation of the recipient and the posttransplantation period despite the use of deltacortisone and heparin, and also lack of experience in this new field of human experimentation.

Despite all this, we managed to draw a certain consolation from this dangerous enterprise: the development of the surgical technique of human transplantation by selecting the retroperitoneal iliopelvic region as the preferred site for renal transplantation; ectopic kidneys, so well known to urologists, are usually well tolerated in this position. This technique has remained the chosen technique in renal reimplantation and later found indications in autologous renal transplantation for the treatment of renovascular hypertension and in extracorporeal renal surgery (29).

"Tamed" Grafts

After these disappointing attempts, I returned to urology and more especially plastic and reconstructive surgery of the urinary tract, in which lesions were considered, at that time, to be irreparable and often responsible for unnecessary nephrectomies or the impossibility of external urinary diversions. At the time, I failed to realize that the progress made in this field of reconstructive surgery would finally result in reliable uretero-ureteral anastomoses and uretero-enterocystoplasties which we subsequently used in renal transplantation. From 1965 onwards we used these various techniques to prepare or repair the excretory tract of the transplanted kidney.

After learning about the astounding success by Murray, Merrill, and Harrison in a case of transplantation performed in a pair of dizygotic twins in January 1959 after sublethal irradiation of the recipient, and another transplantation performed six months later and under the same conditions by Vaysse and Auvert who belonged to the Jean Hamburger team at Hôpital Necker, I again became involved in human renal transplantation, now justified by the development of an immunosuppressive agent capable of inducing tolerance of the graft: irradiation. This modality had already been proposed at the beginning of the century by Alexis Carrel who sensed it to be a means of "reducing the activity of leukocytes, bone marrow, and the spleen, responsible for rejecting antibodies," while the immunosuppressive effects of this irradiation had been recently studied by my friend Dempster.

We didn't have to wait very long before this modality of recipient preparation was put into practice. In 1956, I had performed a left nephrectomy for cancer in a 38 year-old patient, Mr. Coq. I reexamined him in 1959 when he presented with a massive cancer of the remaining kidney with no detectable signs of metastases responsible for end-stage renal failure (blood urea varying between 2 and 2.50 g). His wife begged me to attempt transplantation by offering one of her kidneys. In those days, in the absence of dialysis, such an attempt represented his only chance of survival, even if only slight.

I then sought the help of my colleagues who were leaders in their fields in order to form a team at the Centre Medico-Chirurgical Foch in Suresnes-Paris: Marcel Legrain,[a] a nephrologist who was already a friend of mine and a valuable colleague at the Urology Department of Hôpital Cochin; Georges Mathe,[b] also a longtime friend, Director of the Institute of Oncology and Immunology at Villejuif; Maurice Tubiana, who was head of the Department of Irradiation at the Institut Gustave Roussy, responsible for the irradiation of our patients with the cobalt bomb; Nedey, the intensive care physician, who was subsequently responsible for looking after the patients in brain death and the sterile unit; Vourc'h, an anesthetist, and Camey, Desarménién, and Poisson, forming my surgical team...

Thus, in common agreement, we complied with the wishes of Mrs. Coq. and her husband was transplanted in January 1960, not with his wife's kidney, found to be ABO incompatible, but with his sister's, Mrs. B., six years older than Mr. Coq. and compatible for red blood cell groups, who also eagerly offered her kidney.

Unfortunately, this choice led to a family dispute - which is still continuing today, 30 years after the transplantation - between the frustrated wife "ready to give any of her tissues in order to help her husband" and her sister-in-law, the generous donor. This situation already anticipated the often difficult psychological problems which would be raised in the future with organ donations from a patient's family (32).

A protocol was established and scrupulously applied (4,5):

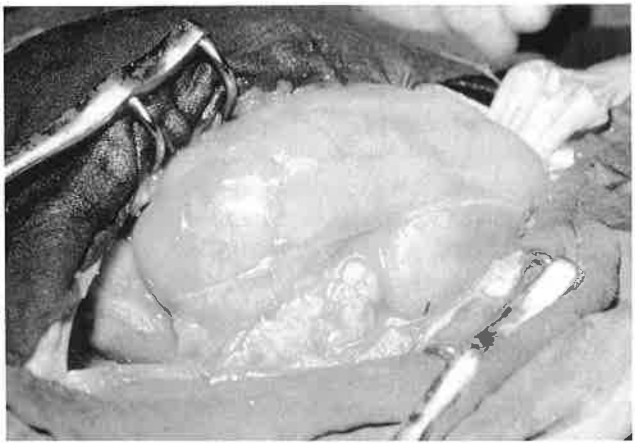
January 12, 1960: Radical nephrectomy for extensive cancer of the remaining right kidney during which, I mention it today, he

---

[a] Marcel Legrain had been Research Fellow for one year at the Peter Bent Brigham Hospital. He had worked with J.P. Merrill and in 1959, performed the first peritoneal dialysis in a transplanted patient. In 1960, he was in charge of hemodialysis and peritoneal dialysis at Hôtel Dieu hospital in Paris.

[b] Georges Mathe, a pioneer of bone marrow transplantation, had contributed, in 1958, in the salvage of accidentally irradiated Yugoslav physicists by performing bone marrow grafts with Léon Schwartzenberg and, in 1959, he performed eight bone marrow grafts in patients with acute lymphoblastic leukemia.

Mr. Coq... Appearance of the tense, swollen, anuric kidney 48 hours after transplantation. Decapsulation.



Transplantation from sister to brother (1-17-60). The recipient, Mr. Coq... at home with his donor sister and his daughter five months after the operation.

received several blood transfusions; absence of lymphadenopathy or hepatic metastases.

January 15: Hemodialysis session.

January 16: Total body irradiation by external cobalt therapy at a sublethal dose of 400 rads (**) with an additional 200 rads applied to the spleen.

January 17: Left renal transplantation into the left iliac fossa (the previous nephrectomy prevented the use of the right iliac fossa) according to the technique developed in 1951 with restoration of urinary tract continuity by uretero-ureteral anastomosis joining the ureter of the graft to the recipient's ureter, still in good condition three years after the nephrectomy, resulting in immediate and abundant diuresis.

Everything was going well until suddenly, 48 hours after the transplantation, the patient developed total anuria with a feeling of pressure experienced over the kidney and a fever of 39°C. Insertion of a catheter eliminated an obstruction of the excretory tract and, in the absence of a precise diagnosis for this anuria, we decided to perform an emergency operation. As soon as we reopened the incision, the appearance of the kidney, turgescent and twice its normal volume, with a free vascular pedicle, immediately suggested acute rejection. I decapsulated the congested kidney in order to release pressure in the tense parenchyma and, miraculously, almost in the same minute, a minute which was the most exhilarating of my career as a surgeon, Dr. Attalah, who was monitoring the ureteral catheter, observed the first drops of urine which became increasingly rapid. Diuresis was restored after five hours of anuria and the early rejection was eliminated.

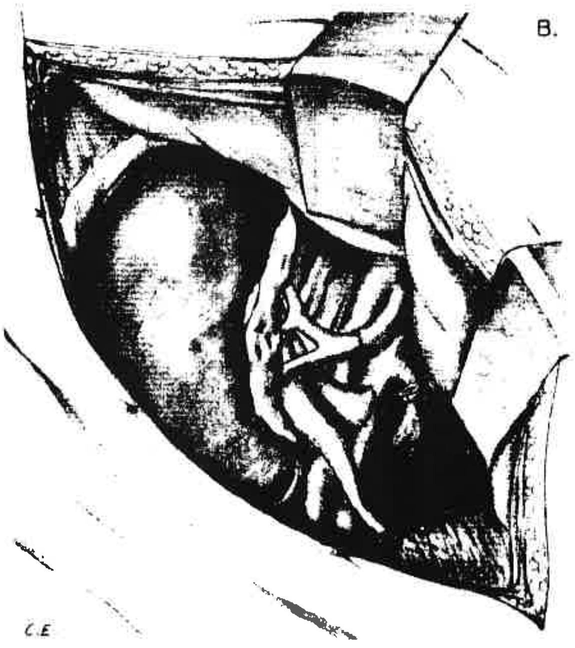
Why did I perform this decapsulation which was seemingly so life-saving? Perhaps because at that time it was the "fashion" amongst doctors in the hope, if only very slight, of correcting secretory anuria, but more especially in this case in order to decompress the tense parenchyma and possibly reduce the role of renal edema, interfering with the venous return. We then performed such a decapsulation for a number of years in order to prevent the effects of renal edema after transplantation. However, a doubt concerning the possible immunological participation in this anuria led to the addition of complementary irradiation of 150 rads to the kidney, already recommended by Hume, but the biopsy results only revealed edema and rare inflammatory cells with no signs of lymphocyte and plasmocyte infiltration.

After a three-week phase of marrow aplasia in the sterile unit, which was certainly very difficult, but not associated with any major complications, the patient returned home. An early clinical and laboratory assessment in the beginning of May was very favorable. Renal function remained unchanged (urea: 0.40 g/l) when, several weeks later, a rapid deterioration in the patient's general status was observed with acute carcinomatosis and multiple hepatic metastases. The patient died at home on May 28. It was not felt "humanely" possible to remove the kidney for histological examination.

This case, although shortened by the development of disseminated metastases, most certainly largely due to the immunodepression of irradiation, demonstrated for the first time that this form of preparation was able to induce tolerance lasting more than five months between non-twin siblings with preservation of good renal function. This situation could no longer be attributed to a possible induction due to an exchange of blood cells during fetal life (Medawar and Owen), as in the two previously reported cases of transplantation in dizygotic twins in Boston and in Paris.

Encouraged by these promising results, largely published in the media and ensued by a flood of requests from patients with renal failure, we attempted another renal transplantation the following month, in June 1960, this time in the absence of any

Transplantation from brother-in-law to sister-in-law on 6-22-60. Mrs. Gen...and her brother-in-law with the Hôpital Foch team, between Marcel Legrain and René Küss.



Surgical technique. Drawing made during the operation on Mrs. Gen...on 6-22-60.

blood relation, between a brother-in-law and a sister-in-law. Soon after, in January 1961, we also had to accept transplantation between husband and wife, as we had almost done one year previously, due to a sufficient familial "compatibility" between the spouses and also in ABO, to justify transplantation.

In June 1960, Mrs. Gen., 26 years old, was referred to us by our friend Rene Wolfromm (nephroimmunologist) with end-stage renal failure (blood urea between 3 and 4 g) due to chronic pyelonephritis with hypertension. After studying renal function and blood groups of all the members of the family who were "ready for anything," her brother-in-law, also very keen to participate, was selected as the best donor. Using the same protocol with total body irradiation of 400 rads, this time in two sessions, and an additional 200 rads to the spleen, the donor's left kidney was transplanted on June 22 into the patient's right iliac fossa. Abundant diuresis was obtained immediately with correction of the blood urea within 36 hours. Five weeks after transplantation, the clinical and laboratory situation excellent up until then, suddenly changed: fever, graft tenderness, and leukopenia suggested rejection which was confirmed by biopsy performed on August 17, showing lymphocyte and plasmocyte infiltration of the kidney with the presence of pyroninophilic cells.

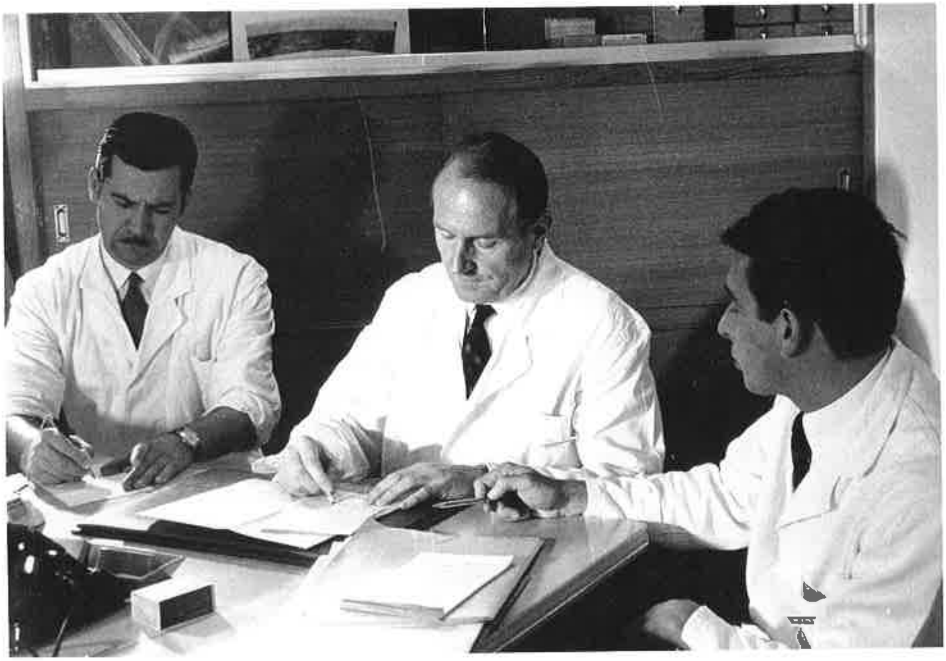
On the basis of the recent results of the experimental studies conducted by Calne, we prescribed 6-mercaptopurine at the dose of 50 mg/day and cortisone at the dose of 40 mg/day. The patient received another session of total body irradiation with a dose of 100 rads, and an additional 100 rads to the graft. The clinical and laboratory effect was remarkable, but almost complete bone marrow aplasia persisted until September and interfered with the immunosuppressive chemotherapy.

At the third month, in a single operation, I had to remove the two small pyelonephritic kidneys (weighing a total of 50 grams) because of a minor urinary tract infection.

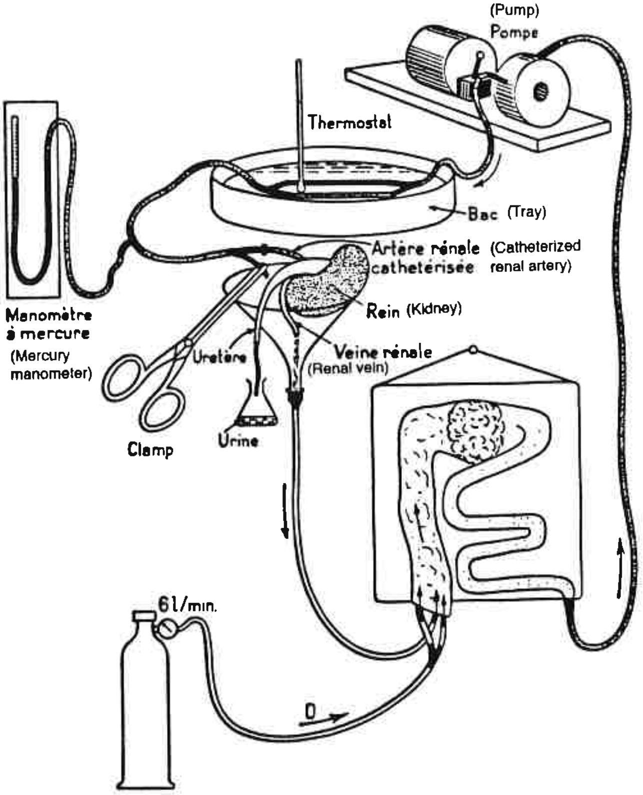
In January 1961, the patient was in excellent clinical condition six months after transplantation, but from March onwards, despite persistence of this good clinical condition, the renal function gradually deteriorated. Immunosuppression, transfusions, etc, failed to induce any improvement, and the patient died in end-stage renal failure on October 25, 1961, ie, 16 months after transplantation. Histological examination of the graft confirmed chronic nephritis with interstitial fibrosis, panarteritis and glomerulosclerosis (6-8).

What conclusions did we draw from this case? It confirmed the efficacy of irradiation for ensuring prolonged tolerance to an unrelated graft for a period of time never previously observed. However, it was not sufficient to prevent rejection, the slow but progressive destruction of the kidney by the host's immune reaction. However, this repeated irradiation, even at low doses, was found to be particularly dangerous in terms of hematopoiesis. This case illustrated, perhaps for the first time, the ability of 6-mercaptopurine combined with cortisone to reverse late rejection. The patient's long survival, despite the absence of any blood relation to the donor, opened the way to a growth in transplantation the magnitude of which could not yet be foreseen.

Hoping to obtain tolerance, we dared - and we later had cause to regret it - to increase the dose of total body irradiation to 600 rads in two sessions in a 36-year-old patient, Mr. M. By, suffering from end-stage renal failure and malignant hypertension complicated by amaurosis. He received a kidney from an ABO-compatible brother. The transplantation was performed on November 6, 1960 according to the usual technique: the left kidney was placed, after inversion, into the contralateral iliac fossa; bilateral nephrectomy was performed at the same time in order to control the hypertension. The immediate postoperative course



René Küss between M. Camey (on the right) and J. Poisson (Hôpital Foch, 1963) 1960-1963. Review of the first 10 transplantations: seven deaths and three prolonged survivals. The morale is low.


(Pump)
Pompe
Thermostat
Bac (Tray)
Artère rénale catheterisée (Catheterized renal artery)
Rein (Kidney)
Veine rénale (Renal vein)
Manomètre à mercure (Mercury manometer)
Uretère
Clamp
Urine
6 l/min.
O

Kidney conservation. Diagram of the apparatus in 1962. Experimental study of kidney conservation by hypothermic pulsatile perfusion of blood.

was uneventful. On the day of the operation, the blood pressure returned to normal, his sight improved and a diuresis of 3 liters was recorded. However, despite the absence of hemorrhagic or infectious complications, the patient died 18 days after transplantation in a severely deteriorated state. Controls showed a normal kidney, total aplasia, and regression of lymphoid formation on the small intestine together with a fistula.

This new case seemed to confirm the efficacy of transplantation and possibly of bilateral nephrectomy in the treatment of malignant hypertension with disseminated vascular lesions, even severe, which do not constitute a contraindication to transplantation. But it also confirmed the fatal danger of irradiation with 600 rads, when 400 rads already represented 50 percent of the lethal dose (9) and was the cause of death in this case.

This unfortunate experience led us to modify our treatment by reducing the irradiation to a dose of 250 rads, while maintaining the graft irradiation (3x100 rads) and by compensating for this reduction by the long-term prescription of 6-mercaptopurine and cortisone.

This protocol was applied in October 1961 in a 38-year-old woman, Mrs. Cha..., with very advanced uremia, who received an unrelated kidney removed from a donor who was undergoing a Matson operation. The clinical and laboratory assessments were very satisfactory (urea: 0.35 g/l) until February 1963, but suddenly, during the month of May, without any warning signs on the regular check-ups, the patient died after several days of acute septicemia with marrow aplasia. Histological examination of the apparently healthy transplanted kidney only revealed discrete signs of cellular infiltration with a few lesions of inflammatory panarteritis.

This new case confirmed the value of this mixed protocol: low-dose irradiation followed by continuous chemotherapy introduced after restoration of hematopoiesis. This combination enabled us to achieve in this case the longest survival (18 months) observed at that time with an unrelated donor kidney. It retained its good function until the patient's death, which was again due to the effects of immunodepression.

This case was certainly a great encouragement for our group to continue in this field, but it also constituted a reason to replace total body irradiation, so painful for our patients and so lethal in its effects, by immunosuppressive drugs (azathioprine and cortisone), already used at Brigham Hospital in Boston after several years of animal experimentation in Joe Murray's laboratory at Harvard, by Calne, and in the following years by Alexandre and then Poisson. Denver, Los Angeles, and Richmond were also starting on this new drug which we had found to be effective in combination with irradiation (8).

In September 1963, a small international committee was held in Washington and was attended by the 20 to 25 pioneer surgeons and physicians working in the field of transplantation. At this meeting, each of us presented the results of his experience which, overall, was fairly disastrous. For our group, out of the 10 transplantations performed since 1960, we registered seven deaths and three prolonged survivals, and our results were not amongst the worst. The review of results caused some of us to doubt the real value of renal transplantation when, at the end of the meeting, a newcomer amongst the group of pioneers, Thomas Starzl, unraveled three rolls of paper which he carried under his arm and raised our hopes by presenting his results obtained with azathioprine and cortisone. Personally very impressed, I accompanied him when he returned to Denver, in the company of Shackman and Poisson, his Fellows at that time. In addition to his operative virtuosity, we were able to appreciate the extraordinary vitality of his group and his already very promising results.

Our confidence restored, but still under the influence of an excessive number of failures, we raised the question as to whether it was still really legitimate to remove kidneys from healthy subjects, whether or not they were related, even when they were volunteers. It was in order to avoid this ethically very dubious mutilation that we deliberately focused our attention on cadaver donor collection, considered to be more rational, although we were well aware of the problems involved in the organization of such procedures and, subsequently, in the legal, social, moral, and economic fields.

However, at this time, transplantation with cadaver kidneys represented a Dantesque adventure recalling that of Michelangelo in Santo Spirito, dissecting cadavers in secrecy at night by candlelight, so eager was he to discover anatomy. The collection of cadaver kidneys raised a variety of reactions and sometimes even opposition in our hospital environment, amongst them doctors and some members of the hospital staff. Although there were already a number of cases of "coma dépasse," individualized by Mollaret and Goulon in 1959 (3,21,22) in intensive care units, it was not yet a question of maintaining them for the purposes of organ removal and death could only be certified after cardiac arrest. So it was in the morgue, in the autopsy room, under very precarious conditions, and with no trained assistance that these donor nephrectomies were performed, compulsorily through a long midline xypho-pubic incision, the only one authorized in cadavers. In order to reduce to a minimum the ischemia time of the graft, the team responsible for organ collection often had to be present - like vultures - at the potential donor's death so that our intensive care physician could minimize anoxia by means of perfusions and oxygen - a very traumatic situation which was sometimes exacerbated by the need to obtain the family's consent for organ donation. I still remember the reply given to me, after long reflection and against his wife's advice, by a man who had just lost his daughter: "Yes, Doctor, I agree if it will save someone else, but... only take one kidney." If I evoke this memory, it is to render the homage which we still owe to these organ collection teams whose thankless and difficult task remained in the background for so long and also to these pioneer organ donors whose sensitivity was severely tested.

And how can we describe the state of potential recipients at end-stage uremic poisoning waiting to receive such grafts except to say that the procedure was sometimes referred to as a virtual "cadaver-to-cadaver" transplantation. However, Carrel had considered renal failure to be a favorable factor for the taking of the graft, a concept recently supported by John Merrill, but there were so many other unfavorable factors to control, starting with the duration of ischemia, mainly in normothermia, doubling or tripling the period of 60 minutes considered to be the upper limit for good restoration of graft function.

Numerous studies were performed at this time to improve the kidney preservation time which we achieved simply by perfusion of cold saline solutions.

By 1962, we had studied experimentally in human or animal kidneys whether it was possible to improve the quality of the graft by pulsatile perfusion of oxygenated blood under hypothermia (14). Unfortunately, renal function ceased after one to two hours of perfusion with a rise in blood pressure and arteriography revealed that this failure was due to vasoconstriction in the renal cortex. In contrast, when the perfusion was limited to 45 minutes and the kidney was subjected to hypothermia, before perfusing the kidney on the machine, renal function could be maintained for several hours. However, these experimental results were considered as not being convincing enough for clinical application, as were those reported by J. Poisson in hyperbaric perfusions on pigs performed at the Jouy-en-Josas center (24), and we had to wait for the work of Ackermann and of Belzer before this method of donor organ preservation could be applied in practice.

Without waiting for these advances and despite the poor results, with, however, certain encouraging results, such as those observed in the case of a young girl in excellent health three years after receiving a cadaver kidney, we continued with this approach which, from 1964 onwards became wonderful with the official recognition of cadaver nephrectomies. They could now be performed in the operating room on patients in a state of brain death "with a beating heart" artificially maintained by assisted ventilation and circulation.

The application of hemodialysis to reequilibrate the recipient and enable him to overcome the posttransplant tubulopathy was a great advance. These advances set the groundwork for "organ donation by any individual wishing to help another suffering individual after his or her death" (18). In 1966, we reported our results when 50 percent of transplantations were performed with cadaver kidneys. This study confirmed the considerable difference between the results obtained with "abandoned" cadaver kidneys with total ischemia lasting 75 to 300 minutes, with those obtained from "assisted" cadavers in brain death with an ischemia time of 35 to 60 minutes mostly in hypothermia at $4^{\circ}C$. They resembled the results obtained with living-related donors or with "free" kidneys (25,28).

This considerable improvement, obtained as a result of our strategy, promoted the development of transplantation with cadaver kidneys and the expansion of transplantation to such a point that it raised the problem of finding enough kidneys to satisfy the growing demands.

It was in order to resolve these problems that, in 1967, with Poisson, we set up the "Paris Transplant," an organization designed to collect kidneys from "brain-dead" patients from various intensive care units to satisfy the demands for transplantation, which involved the training of teams of organ collectors on call 24 hours a day in coordination with the Necker and Broussais hospital groups in Paris. These cadaver nephrectomies, soon to be associated with removal of the heart and liver for use by the French pioneers in these new fields of transplantation, presumably made Paris-Transplant the leading center for multiorgan procurement.

In recalling my experience, being at the time always preoccupied by the lack of kidneys, I have to mention an attempt of a xenograft performed in 1966 in a man with end-stage renal failure due to renal stones. We performed "en bloc" transplantation of the two kidneys from a pig, an animal which had not been used since 1906 by Jaboulay, but which was considered to be close to man (24), and which our friend Georges Mathe was using for so-called "third man" skin grafts in the search for histocompatibility. As soon as the clamps were released, the kidneys became very enlarged and violaceous, an appearance which we had previously observed when performing crossed transplantation in animals with human cadaver kidneys. An intravascular coagulation syndrome developed with multiple hemorrhages which were difficult to control by means of abundant blood transfusions. The patient developed hyperacute rejection and the kidneys were removed after 48 hours in the patient's bed, shortly before he died.

Somewhat less fortunate than Reemtsma's and Starzl's trials of animal grafts in man using anthropoid donors, I retained from this painful experience a xenophobia for xenografts which remains with me today!

In 1967, transplantation was on the program of the Fourteenth International Urology Congress held in March (29). This was an occasion to reunite the fraternity of urologist-transplanters (Goodwin, Kauf-

Hôpital Foch, 1968. Confidence is restored. R. Küss amongst seven transplanted patients, including four who have survived for more than three years.

Honfleur, 1965.
J. Merrill is also interested. R. Küss and daughters.

mann, Walsh, Harrison, Shackman...) and to present the experience from different countries. J. Poisson, Auvert, Denis and I reported the French experience obtained at two centers, Necker and Foch, with a total of 101 cases of transplantation. The world leaders in transplantation (Hume, Merrill, Starzl, Woodruff, and several others) were obviously invited to these discussions. At the conclusion of the Congress during which all of the problems had been raised and discussed, we were able to evaluate the progress made since our previous small meeting in Washington. However, the failure rate was still on the order of 50 percent. I privately asked Starzl, Dausset, and Merrill what they considered to be the paths of future progress.

Thomas Starzl thought that progress would depend on the immunodepressive preparation of patients and he presented the preliminary promising clinical results which he had obtained with antilymphocyte serum (ALS), previously experimented by Woodruff and introduced into France by Traeger's and Perrin's team in Lyon.

Jean Dausset's opinion was that progress involved the search for improved histocompatibility between the donor and the recipient by taking into account leukocyte antigens: the HU1 system, which was soon to become the HLA system developed with Ceppellini, Van Rood, and Terasaki and appeared to influence the success rate of grafts.

John Merrill thought that the results would be improved simply as a matter of "know-how" involving all aspects of transplantation, but mainly in the handling of drugs.

Only the future would confirm the validity of these three objectives. I will describe how each of these three aspects evolved in our experience during this period between 1967 and 1972, which represented the period of consecration and diffusion of renal transplantation.

In relation to methods of immunosuppression, after abandoning total body irradiation, we relied on the combination of azathioprine-cortisone, while nevertheless conserving irradiation of the spleen which, following the work by Hume and Starzl, was replaced by splenectomy. However, the increased incidence of infectious complications following splenectomy subsequently led us to abandon this adjunctive method, the efficacy of which has never in fact been demonstrated.

Our initiation to ALS (applied in 51 cases of transplantation) was not entirely satisfactory (30), probably because of the poor quality of the serum available at that time and responsible for frequent adverse reactions which made it difficult to monitor the graft. We abandoned it and subsequently reintroduced it successfully following an improvement in its preparation.

For the search for improved tissue compatibility, our patients were typed for erythrocytes and leukocytes in Jean Dausset's laboratories. A study of 72 transplantations performed between 1965 and 1972, two-thirds of them using cadaver kidneys, failed to reveal any statistically significant differences after one year, and sometimes several years, in terms of the quality of renal function or the severity of extrarenal complications, according to the degree of compatibility of the HLA system (30,31). Poor histocompatibility did not constitute a reason to refuse transplantation which was based on evaluation of the ABO system and on crossmatch, which Terasaki had shown to be essential in the prevention of early rejection.

As for the "know-how" considered by our friend Merrill to be a factor of progress, it demonstrated a very important participation in the improvement of our group's results. A better understanding of the pathophysiology of the graft and the recipient allowed us to more clearly define, in particular, those cases of "mixed rejection" consisting of a combination of immune reaction and tubulopathy and occasionally an infectious process. These "handicapped" transplant recipients raised the difficult problem of the possible advantages of either continuing or changing drug treatment, while placing the patient's life in jeopardy and resulting in a severely impaired kidney, or opting for sacrifice of the graft with return of the patient to hemodialysis and the possibility of a second graft, with which we had already obtained satisfactory results from 1965 onwards. From our observation of this critical period with a complication rate of about 40% during the first weeks, we defined the "three-month critical line" which, once past, indicated a good prognosis for the future of the graft. It was also at this time, faced with the persistent difficulty and the importance of early recognition of rejection, that we first introduced intravenous pyelography in order to detect rejection in the form of a "decapitated kidney," as the calices were rendered invisible by compression due to edema (34).

Although our surgical technique for transplantation had only changed very slightly since 1951, it had been greatly improved by variants adapted to new situations (23). For example, as early as 1964, we also performed upper iliac transplantation as an alternative to pelvic transplantation (following Starzl, Goodwin, and Reemtsma) which provided a vast recipient site for an adult kidney transplanted in a child or for two child kidneys transplanted "en bloc" in an adult, with anastomosis onto the iliac vessels or the aortico-caval axis (18). Taking advantage of the removal of the kidneys and spleen, in 1965, I developed and reported what were perhaps the first successful "in situ" transplantations in the lumbar region (18) by anastomosing the graft vessels to the pedicle of the resected kidney or to the splenic vessels. However, the technical difficulties encountered during reoperation in this deep site of the graft led us to abandon this form of transplantation considered to be "ideal" for a urologist and which was subsequently reintroduced by Gil-Vernet.

In answer to the question of whether or not bilateral nephrectomy in the recipient should be performed at the same time as the transplantation, we were very quick in giving a positive answer and continued with this approach, possibly encouraged by the fact that, at the beginning of our experience, our patients transplanted in urology units generally had pyelonephritic kidneys likely to cause infectious complications in an immunosuppressed context and required secondary nephrectomy, as we have seen above.

At this time, there was a controversy amongst transplanters concerning the choice of technique for restoration of continuity of the urinary tract between uretero-ureteral anastomosis and uretovesical implantation, as the urinary tract complications (fistula and stenosis) were still responsible for a high morbidity. A radiodynamic study of the transplanted kidney performed during the first posttransplant days showed me that, in contrast with what one would expect to find in this denervated kidney, there were no signs of atony, but rather hypertonia with hyperperistalsis of the excretory tract (20). This finding explained the usually good quality of the urine excretion of the graft. However, we observed a number of fistulae which were considered to be due to ischemia, operative technique, or immune rejection of the urinary tract. In one case of vesical implantation of the graft ureter, I was able to confirm this last etiology by endoscopic and histological exploration and by the dramatic effect of antirejection treatment. Vesical implantation with tunnel formation, adopted by many transplanters, probably provided better protection in the case of dehiscence due to rejection than end-to-end ureteral anastomosis, to which I nevertheless remained faithful.

In view of the multidisciplinary nature of transplantation, in 1971 I created the French Transplantation Society, the first of its kind in Europe, in order to group the various specialists interested in and contributing to the development of transplantation - surgeons, physicians, immunogeneticists, intensive care physicians, coordinators - to allow comparison of results in our country as well as exchanges with other European countries, whose leaders in the field (Woodruff, Shackman, Calne, Walsh, Roehl, Alexandre, and others) honored us with their membership. I still remember that famous meeting in November 1971 during which my friend Shackman - who, amongst other things, introduced me to real whisky in his cottage in London - presented a paper on the advantages of blood transfusions performed prior to transplantation. This constituted a veritable scandal for our immunologists who condemned these transfusions as being responsible for preimmunization and, as a result of their verdict, put an end to the project I had developed for massive donor-specific blood transfusions prior to transplantation. However, several years later, Opelz restored these transfusions to their privileged place: they were integrated into the protocols of nearly all transplantation teams and were attributed an important role in the improvement of results.

In 1972, our transplantation unit at Hôpital Foch moved to the Pitie-Salpetriere - the largest hospital center in Europe - where it acquired larger premises, adjacent to the urology, nephrology, hemodialysis, neurosurgery, and intensive care units, with a branch at Hôpital Tenon, directed by J. Poisson. Our renal transplantation activity increased with the arrival on our team of Philippe Thibault who had spent a year in San Francisco with Kuntz and Belzer (who persuaded me to acquire Belzer's machine for prolonging kidney preservation) and later with the arrival of Philippe Frantz who, in 1978, achieved the figure of 75 transplantations in our group, the record in our country.

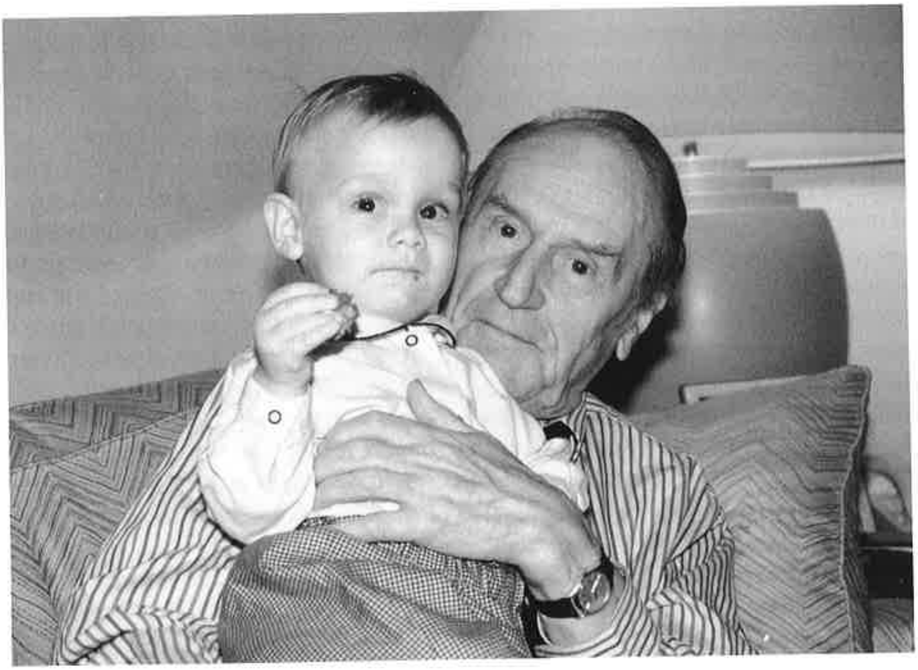
During this period, still in close collaboration with M. Legrain, in the context of the National Hemodialysis and Transplantation Commission, we contributed to the inclusion and organization of various ethical, legal, social, and economic aspects of transplantation in our social context in order to establish new laws controlling, amongst other things, the definition of "brain death" and the collection of cadaver kidneys.

At the same time, Paris-Transplant was succeeded by France-Transplant, founded by Jean Dausset, which developed functional relations with other European organizations and which was responsible for testing, in their laboratories, tissue groups of potential donors in order to direct the kidneys to the most compatible recipients amongst hemodialyzed patients waiting for a graft. These top level organizations, both in terms of immunological research and communication, carried out their mission with the support of public utilities and the various means of transport (road, rail, and air) made available to them.

However, already by 1975, despite these organizations, the dialysis centers of France suffered from a shortage of cadaver kidneys which represented more than 90 percent of transplantations in France. Our unit at La Pitie hospital was privileged by the number of kidneys available due to the presence, in the same hospital complex, of major neurosurgery and intensive care units "which understood how badly we needed kidneys," and we watched, not without a certain bitterness, the departure of these travelling kidneys to be transplanted elsewhere, which led to a certain loss of motivation amongst our teams responsible for kidney collection.

Nevertheless, our experience of the kidneys removed and grafted on site at La Pitie, without setting great store on the degree of HLA compatibility, showed that our results were at least as good if not better

R. Küss and J. Murray at the T. Starzl Jubilee in Pittsburgh in September 1987. Transplanters can also talk with their hands (photo taken by Terasaki).



René Küss, grandfather.

than those obtained with "identified dispatched kidneys" received from France-Transplant, which led us to consider that the advantages in terms of tolerance obtained with an increased degree of histocompatibility were counterbalanced by the advantages of local or regional transplantation. This decision by our group was the basis for a certain "kidney war" and academic sparring matches based on "incompatible" statistics and was still going on in 1981 (34).

A great deal of water has flowed under the bridges of the Seine over the years, and it is now as a spectator that I watch the growth in organ transplantation for which the kidney constituted the launching pad, suffering from a mortality of 90 percent at its beginnings in 1960 to 1962 and enjoying a 90 percent survival rate at the present time.

Recalling today, over the years and not necessarily in order, the memories of what I lived during the "historic and heroic" period of renal transplantation, has been a great pleasure to me, mixed with a certain emotion. This return to basics also offered an occasion to render homage to those pioneers, led by Carrel, who, at the turn of the century, had predicted its realization and also to the large family of transplanters who, from all over the world, have combined their efforts, inspired by the same feelings of confidence in achievement and with whom our group shared the bitterness of failure and the joy of success. This homage must not neglect those of our friends who are no longer amongst us and who made such a valuable contribution to the success of this great adventure... an adventure which continues today with the hope, as a result of progress in the years to come, that the transplanted patient will no longer be "depressed" and that the diseases leading to transplantation will eventually be conquered.

to be continued........

REFERENCES

1. Küss R, Teinturier J, Milliez P. Quelques essais de greffe du rein chez l'homme. Mémoires Académie de Chirurgie, 77, n° 22-23, 755-768, 1951.

2. Küss R. Greffes de reins. Entretiens de Bichat, Vol. CHI. 1952.

3. Mollaret, Goulon M. Le coma dépassé. Rev Neurol 101, 3, 1959.

4. Küss R, Legrain M, Mathe, et al. Prémices d'une homo-transplantation rénale de soeur à frère non jumeaux. La Presse Médicale 68è année, n° 20, 23 avril 1960, 755-760, 1960.

5. Küss R, Legrain M, Mathe G, Nedey. Epilogue d'une homo-transplantation rénale de soeur à frère non jumeaux. La Presse Médicale, 68° année, n° 40, 1473, 1960.

6. Küss R, Legrain M, Mathe G, et al. Deux homo-transplantations rénales chez l'homme. Etude des accidents évolutifs du transplant. 1er Congrès International de Néphrologie, Genève-Evian, 507-516, 1960.

7. Küss R, Legrain M, Camey M, et al. Homo-transplantation rénale chez l'homme. A propos de 3 cas. Mémoires Académie de Chirurgie 87, 183-199, 1961.

8. Küss R, Legrain M. Homologous transplantation of the human kidney. Experiences with four patients. Trans Amer Soc Artif Int Organs 1961; 7:166.

9. Küss R, Legrain M, Mathey, et al. Etude de 4 cas d'irradiation totale par le cobalt radio-actif préalable à une transplantation rénale allogénique. Revue Française d'Etudes Cliniques et Biolopgiques, n° 10, 7, 1028-1047, 1962.

10. Küss R, Legrain M, Mathey, Camey. Homo-transplantation rénale chez l'homme hors de tout lien de parenté. Survie jusqu'au 17ème mois. Revue Française d'Etudes Cliniques et Biologiques, n° 10, 7, 1048-1066, 1962.

11. Küss R, Legrain M, Mathey, et al. Homologous human kidney transplantation expérience with six patients. Postgraduate Medical Journal, 38, 528-532, 1962.

12. Mathe G, Amiel JL. La Greffe. Aspects biologiques et cliniques. Masson et Cie, 1962.

13. Küss R. Un expérience de transplantation rénale chez l'homme. A propos de 16 cas. Extrait des Journées de Médecine Internationale deVérone. 12-13-14 septembre 1963.

14. Küss R, Dimopoulos, Langlois, Labbe. Contribution à la préparation du rein de cadavre en vue de conservation pour homo-transplantation. Revue Française d'Etudes Cliniques et Biologiques, 8, n° 10, 1024-1032, 1963.

15. Küss R, Legrain M, Mathe G, et al. Nouvel essai de transplantation rénale hors de tout lien de parenté. Evolution favorable au quinzième mois. Société Médicale des Hôpitaux de Paris 114, n° 3, 230-238, 1963.

16. Poisson J. Les homo-transplantations rénales en 1964. Progrès réalisés. Problèmes acuels, perspectives d'avenir. Thése de Paris, 1963.

17. Küss R, Legrain M, Coll. Le problème de la tolérance aux greffes allogéniques chez l'homme, étudié par la transplantatin de rein. Colloque C.N.R.S. sur la greffe des cellules hématopoïétiques allogéniques, 235-241, Ed. CNRS, 1964.

18. Küss R, Poisson J. Actualité de l'homo-transplantation rénale chez l'homme. Europa Medica, n° 4, 210-219, 1965.

19. Küss R. Réflexions sur l'homo-transplantation rénale chez l'homme. Lyon Chirurgical, 62, 116-120, 1966.

20. Bredoux J. Contribution à l'étude de la physiopathogie de la voie excrétrice du transplant rénal. Thèse, Paris 1966.

21. Goulon M. Le coma dépassé et le coma avec sidérations végétatives transitoire. Marseille Chir. 18, 18, 1966.

22. Nedey R. Le coma dépassé (stade IV). 40 observatins personnelles. Marseile Chir. 18, 137, 1966.

23. Küss R, Camey M, Poisson J, Chatelain C. Aspects chirurgicaux de l'homo-transplantation rénale chez l'homme. Mémoires Académie de Chirurgie, 92, n° 22, 624-636, 1966.

24. Podliachou K, Modeyska-Lewandoska, Poisson J. Contribution à l'étude des groupes sanguins de porcs. Recherche expérimentale sur l'hétérotransplantation. Revue Française d'Etudes Cliniques et Biologiques, n° 10, 7, 1028-1047, 1962.

25. Küss R, Legrain M, Poisson J, et al. Problèmes posés par la transplantation de reins de cadavre. European Dialysis and Transplantation Association, Lyon, France, juin 1966.

26. Basile M. L'omotrapianto renale umano. Patron. Bologne, 1966.

27. Küss R, Legrain M, Nedey R, et al. Perspectives offertes par l'homo-transplantation rénale hors du lien de parenté. La Presse Médicale, 75, n° 2, 59-64, 1967.

28. Küss R, Poisson J. A propos du prélèvement des reins de cadavre. Mémoires de l'Académie de Chirurgie, 93, n° 28-29, 859-863, 1967.

29. Poisson J, Küss R, Auvert J, Denis M. Expérience Française de la transplantation rénale. 14ème Congrès Int Urol 181-229, Munich 1967.

30. Küss R, Legrain M, Gluckman JC, Thibault PH. Allotransplantation rénale chez l'homme. Méthodes de conditionnement et analyse des complications à partir de 72 cas dont 51 ont reçu des globulines anti-lymphocytes. Minerva Chirurgica, 26, n° 13, 721-734, 1971.

31. Küss R, Legrain M, Gluckman JC, et al. Allotransplantation rénale chez l'homme. Résultats et prospective à partir de 72 observations. La Presse Médicale, 79, n°43, 1971.

32. Valiere H. Remarques pour l'élaboration et la mise en place d'un soutien psychothérapique des transplantations rénales. Rev Méd Psychosomatique et de Psychologie médicale, n°1, 31-46, 1971.

33. Küss R, Poisson J, Le Guillou M. L'urographie intra-veineuse au cours de la crise de rejet dutransplant. Son intérêt diagnostique. Journal d'Urologie et de Néphrologie, n° 7-8, 605-613, 1973.

34. Küss R, Viars P, Frantz PH, et al. Les prélèvements de reins encore insuffisants: vers une régionalisation de la transplantation. Bull Acad Nat Méd, 81, n°3, 301-394, 1981.

CURRICULUM VITAE

René Küss

PERSONAL

Born: 1913; Paris

POSITIONS

1944	Anatomy Prosector, Faculty of Medicine, Paris
1949	Professor of Urology, Faculty of Medicine, Paris
1950	Surgeon in the Hospitals of Paris
1953	Urological Surgeon, Hôpital Foch, Head of the Renal Transplantation Unit (1960-72)
1960	Surgeon at Hôpital Saint Louis
1964	Professor of Surgical Pathology
1972	Professor in the Urology Clinic and Head of the Renal Transplantation Unit from 1972-73, Pitié-Salpêtrière University Hospital
1988	Emeritus Professor, University of Paris VI

PROFESSIONAL SOCIETIES

1960	Member, French Academy of Surgery
1971	Founder and President, French Transplantation Society
1975	Member, French National Commission of Hemodialysis and Transplantation
	Honorary President of France-Transplant
	Member, International Transplantation Society
1978	Founder and President, Department of Oncology at Pitié-Salpêtrière
1979	Founder and President, International Conference on Urinary Tract Cancers in Paris
1979-85	President, International Urology Society
1979	President, International Urology Congress
1980	President, French Surgery Congress
1987	President, French National Academy of Medicine
1988	President, "Foundation-Transplantation Alsace"

AWARDS

1939-40	Doctor, 1st Class in the French Navy (Croix de Guerre avec Palme)
1944	Captain, Head of surgical team (7th American Army)
1974	Officier of the Légion d'Honneur
1977	Carnegie Foundation Silver Medal
1979	Commander of the National Order of Merit

PUBLICATIONS

Numerous books, texts, films, foreign missions and conferences... essentiallyon the following subjects:

- Genitourinary tuberculosis
- Plastic and reconstructive surgery of the urinary tract
- Renal transplantation
- Cancers of the genitourinary apparatus
- Embolization in urology
- Transsexualism

"Illustrated History of Urology from Antiquity to the present day" with Willy Gregoir (1989) Da Costa Ed.

"Illustrated History of Organ Transplantation" (in preparation - 1992)

OUTSIDE OF UNIVERSITY HOSPITAL ACTIVITIES

Aspects and functioning of Social Security in Europe

Report to the New York Academy of Medicine in 1983: "100 years of Social Security (1883-1983)"

MEMORIES OF OLD TIMES

Jean Hamburger

Address: Académiedes des Sciences
23 quai Conti
75006, Paris, France

Jean Hamburger

1963

1990

MEMORIES OF OLD TIMES

Jean Hamburger

Paris, Christmas Eve 1952

December 1952. A young carpenter 16 years of age, Marius R., was sent to Necker Hospital, where I was in charge of the nephrology service. The boy was anuric. He had fallen from a scaffolding and ruptured his right kidney. The kidney had to be removed but after the operation, the patient passed no more urine. We discovered that he had congenital absence of the left kidney. He was now anephric. Repeated dialysis with the artificial kidney had not yet been developed. Because my research team had been carrying out experiments in kidney grafting for several years, the question of renal transplantation was raised. The boy's mother pleaded with us to attempt to transplant one of her kidneys to her son.

We knew that genetic factors played an essential role in graft tolerance in animals. The close immunological relationship between mother and son seemed, in our ignorance at that time, to be confirmed when we found that they shared the same major and six minor red blood groups. On the other hand, we knew that the actual surgery presented no problem. The operative technique had been established by surgeons such as René Kuss and Jean Vaysse in France, and David Hume and Joseph Murray in the United States.

Our doubts and hesitation can be imagined, but finally we decided that to turn a deaf ear to the pleas of the family would be no less reprehensible than to agree. On Christmas Eve 1952, a surgical team composed of a urologist (Louis Michon) and two vascular surgeons (Jean Vaysse and Nicolas Oeconomos), removed the mother's left kidney and transplanted it into the right iliac fossa of her son.

The grafted kidney functioned immediately. In the following weeks we had high hopes for success. The boy's blood urea fell to normal and his general condition improved to the point where he was able to be up and about. On the 22nd day rejection set in with sudden arrest of kidney function. This may have been, to start with, only a transplant crisis (such as I described later) that can be reversed with suitable treatment, but this knowledge lay in the future. The length of time that the graft was tolerated was, however, at variance with all previous experience. We were confirmed in the hypothesis that, in man as in animals, genetic relationship could favor tolerance. We went on to consider the possibility of achieving indefinite prolonged tolerance in similar cases by depressing the immunological reaction of the recipient to some degree. We had to go back to the animal experiments that we had been performing for several years.

Experimental Data: November 1947

Five years prior to the story I have just related, I had published the experimental results presented to the French Society of Urology on November 17, 1947 in the *Journal d'Urologie*. Renal transplantation had been performed on dogs and pigs by Oudot, a young French surgeon. Mice had also been used for the study of skin grafts. The grafted kidneys functioned for varying periods of time but in all cases were eventually rejected. The rejection seemed more rapid when the donor and the recipient dogs belonged to different breeds, suggesting that genetic factors influenced the renal graft tolerance exactly as it usually did in mouse skin grafting. We also found that cooling the kidney during its transfer from donor to recipient improved the results.

Reviewing all known data at that time, I concluded that three obstacles had to be overcome in order to achieve successful kidney transplantation in man: a) efficient protective measures against the deleterious effects of ischemia on the kidney removed from the donor should be found; b) tissue compatibility groups should be found and applied to transplantation, in the same way that blood groups allowed blood transfusion; and c) the discovery of antirejection techniques or drugs was necessary. These conclusions, more or less, were a prediction of what was to occur in the following years.

In 1952, the same year that Marius R. had been transplanted, Frank Dixon and his collaborators published evidence in the *Journal of Immunology* that immune reactions could be depressed in rabbits by using x-rays. French radiotherapy experts such as Claude M. Lalanne, Maurice Tubiana and others, had acquired considerable experience in total body irradiation techniques for certain malignant blood disorders. It was tempting to apply this method to the problem of transplantation and, indeed, this was suggested by W. J. Dempster in London. We had become familiar with the consequences of total body irradiation in man through an episode which took place in 1958:

On October 6, 1958, six Yugoslavs working in the nuclear center of Vinca near Belgrade were severely irradiated following an incident in the nuclear reactor. They were transported to Paris and we participated in their follow-up and treatment. White cells and platelets almost completely disappeared from their blood, together with a diminution of the number of red cells. However, four weeks after the accident, bone marrow and blood were progressively repopulated and all patients except one recovered. During the critical period, they had been protected from microbial contamination in so-called "aseptic" rooms.

Similar cases had been reported in the literature. It seemed that a radiation dose around 350 rads could induce severe but curable bone marrow depression and perhaps prevent graft rejection.

Animal experiments, however, gave very inconsistent results, and we might never have gone on to attempt the procedure in man but for the influence of John P. Merrill.

1959: The Crucial Year

John had come to spend a sabbatical year in Paris and we soon fell under the spell of this patrician Bostonian with the inquiring mind, who was firmly convinced that desperate diseases called for daring remedies. One day, during a discussion about the new and difficult ethical problems of kidney transplantation in man, he said: "Your fears and hesitant attitude seem wrong to me. Think of all the patients who may die in the future because you have not had the courage to do what was necessary to add to our knowledge and open the way to new methods of treatment." But in France, as elsewhere, the idea was, and indeed still is, deeply rooted: no treatment is acceptable unless it benefits the patient himself as an individual, and it can never be justified merely to further medical knowledge.

Early in 1959, John Merrill tried a kidney graft between nonidentical twins after irradiating the recipient. One of our patients in terminal renal failure, George S., also had a nonidentical twin who had volunteered to donate a kidney. We decided that our scruples were no longer justified in view of the good immediate results of the Boston case. So we in turn performed a graft on George S., using cobalt therapy for immune depression.

George S. was a 37-year-old post office worker diagnosed with chronic nephritis in 1951. His kidney deterioration was progressive, and by 1959, when he had reached a stage of terminal and threatening renal failure, he told us that he had a twin brother who was willing to donate a kidney. He knew that successful transplantation had been achieved between identical twins. Unfortunately, as soon as we saw the brother, on the basis of their physical appearance we suspected that they were not identical twins. A series of tests confirmed that they were nonidentical twins, therefore they could not benefit from the usual absence of graft rejection observed between identical twins. I was reluctant to proceed. However, we noted two facts suggesting that the brothers had a close genetic relationship: a) a skin graft from the patient to his brother was not rejected until the 25th day, a longer time than usual; b) the leukocyte test mentioned above gave identical results in both men (some years later, we were able to confirm that they were HLA identical, but the word did not yet exist). Finally, as mentioned before, we knew that the Boston group had just performed a renal transplantation in a similar case and through repeated transatlantic telephone conversations, we learned that the first postoperative weeks were very encouraging. I then thought it possible to undertake the transplantation so keenly desired by George S. and his brother.

Within a few days we improvised a sterile unit. The room received filtered air under positive pressure through a special air conditioning system. The unit was equipped with powerful bactericidal ultraviolet lamps. The microbial content of the air in the unit was found to be one percent of that measured in the hospital courtyard. Doctors and nurses, wearing sterile boots, white coats, caps, and gloves, entered through an airlock. A bacteriologist constantly supervised the entire process.

Total irradiation of the patient was performed with radioactive cobalt in two sessions on June 22 and 28. Surgery took place on June 29. Blood circulation in the kidney was interrupted during 40 minutes. Soon after, the first drops of urine appeared at the extremity of the ureter, which was then implanted in the patients's bladder.

Although blood urea and creatinine had dropped to normal nine days later and everything seemed satisfactory, we were not without anxiety. Suddenly, on July 13, the urine volume decreased, blood creatinine rose, and the specter of rejection loomed before us. Yet, on July 20, the grafted kidney spontaneously recovered normal and stable function.

Despite the fact that our case was published during that year, 1959 (four months after the operation), whereas the Boston case did not appear in print until 1960, John Merrill's initiative was not only first in point of time, but was the determining factor in our own case. Both the Bostonian and the Parisian patients were to remain perfectly healthy with well-functioning grafted kidneys.

It was, however, suggested that these two initial successes might be due to some peculiarity of the nonidentical twins. From Owen's work it was known that it is not uncommon in animals for binovular twins to acquire reciprocal tolerance during fetal life. Thus, they can form "chimera" in which two types of red blood cells, those of the animal itself and those of its nonidentical twin, are found side by side. It was suggested that something of the sort might have happened in the two cases described above. Were these mere curiosities or did they point the way to a solution of the problem of organ grafting in general?

The Sixties: Where the Ways Part

For many reasons, particularly the absence of any detectable blood chimerism and the rejection by one of the binovular twins of a skin graft from the other, we concluded that the real reason for the success was the close genetic relationship of donor and recipient. From this followed the necessity of discovering means of donor selection and of assessing the degree of immunologic similarity between donor and recipient. This was the parting of the ways between the Boston group and us. At that time, they were more than skeptical about the very principle of selecting the donor on an immunological basis. I received a letter from John Merrill predicting that I would reach a dead end. He turned all his efforts to the discovery of new methods of immunosuppression while we were concentrating on immunologic donor selection. In our case, this led to collaboration with a man who was to play a decisive part in the orientation of our thinking, Jean Dausset.

Jean's laboratory was, at that time, located in the same hospital group as ours. With admirable intelligence and tenacity, he had established that white blood cells carry "isoantigens" which differ from one individual to another. It was tempting to suppose that this might provide a method for comparing the immunologic characteristics of the donor with the recipient of a graft. Everyone throughout the world knows the remarkable development of this line of research. The story is related in another book edited by Paul Terasaki, *History of HLA: Ten Recollections*.

We were probably the first to apply the study of histocompatibility to making the choice of a donor. It is reasonable to think that this decision was responsible for the fact that the first successful renal transplantation between nontwins was obtained in our group rather than elsewhere.

February 12, 1962: The First Successful Transplantation Between Nontwins

An 18-year-old boy, Jean V., was dying of renal failure due to nephrophthisis, a ter-

Three of the first successfully transplanted patients. The patient in the middle had received a kidney from a nonidentical twin. The patient on the right is the first world permanently successful recipient with a nontwin donor: He is alive and well today, 28 years later. The patient on the left received a kidney from an identical twin.

rible disease described some years earlier by René Habib in our hospital. Many members of the young patient's family volunteered to donate a kidney; so we studied their leukocyte groups, in so far as they were detectable with the methods of that time. It so happened that they were found identical to the patient in a young woman who was his first cousin. As was our custom in such cases, we made sure that she had received no external pressure from the family and that she was aware of the risk she ran and the uncertain outcome of the graft. She was indeed a genuine volunteer, and we decided to accept her offer.

The transplantation was performed on February 12, 1962. The patient is still in good condition, almost 30 years later. He was so impressed by the whole event that he decided to study medicine and became a cardiologist in a French provincial town where he is still practicing.

During the same year René Küss, Marcel Legrain, and others published six cases of renal allotransplantation following total body irradiation. Immediate failure followed in four cases, two of them had prolonged tolerance, but, as far as I know, permanent tolerance was achieved in none of these cases.

October 10, 1964: The First Successful Cadaver Kidney Transplantation

Thirty-year-old Yvette T. was admitted to the Necker Hospital in the final stage of chronic glomerulonephritis on September 24, 1964. We knew her well since she had been hospitalized more than 12 times during the previous 12 years. We had been helpless witnesses to the progressive aggravation of her renal insufficiency. She was now practically unconscious, vomiting, almost blind, and heart auscultation revealed severe pericarditis. Dialysis with the artificial kidney improved the situation, but it was clear that the best solution would be renal transplantation.

On October 9, we were informed that a 43-year-old man in another Paris hospital was dying from irreversible brain damage following cerebral hemorrhage. His survival was being artificially prolonged by mechanical ventilation and maintenance of blood volume. The blood group was identical to that of our patient and the comparison of leukocyte groups was satisfactory. On the following day, after several flat EEG readings, the man was recognized as dead and a death certificate was signed. The possibility of transplanting one of his kidneys to our patient was then considered. The family of the deceased was approached and made no objection. We asked the doctors in charge to maintain a certain degree of oxygenation in the cadaver with artificial ventilation. Yvette T. was transported to the hospital where the donor lay and at 9 PM the kidney was removed, perfused with a special solution at 4°C and kept in an icebox until transplantation. The time of kidney ischemia between removal and restoration of blood circulation in the kidney was 64 minutes. Yvette is in perfect health, active and happy, 26 years later. This is probably the oldest case of a cadaver kidney recipient still alive today.

The Following Years: The Graft Boom

During the following years the number of renal grafts rapidly increased in my department, while we were pleased to see many other groups in France and throughout the world enter into the game. We met with successes and failures. Year after year we learned more about the care of these patients. Effective immunosuppressive drugs were now available and had replaced the initial use of x-rays. As early as 1964 I described the "reversible rejection" or "transplant crisis" and found that

Jean Hamburger receiving the Honorary Fellowship of the American College of Physicians (April 1974).

Jean Hamburger discussing with Sir Peter Medawar (August 1982).

Jean Hamburger wearing the green coat of French Academicians, a uniform of black cloth, embroidered with olive leaf clusters of silk. He was elected in 1974 as a member of the French "Académie des Sciences" of which he is now President.

high doses of corticosteroids could cure most of these episodes. This was soon confirmed by others. We also found simple and efficient methods for the preservation of the kidney during its transfer from the donor to the recipient. The whole history of the grafted kidney, clinical and pathological, was written by us and others. An unprecedented international effort was devoted to the HLA system. The importance of histocompatibility testing, which we had predicted from the very beginning, was slowly confirmed. New drugs, new tests, better plans for management and follow-up of grafted patients were developed. The percentage of successes rose progressively toward 90 percent of cases. Thousands of patient's lives were now saved by renal grafting. And the transplantation of other organs became possible using methods similar to those we and others had described for the kidney.

Jean Hamburger in the office in which he works and writes, 1990.

At the same time, unexpected consequences of transplantation research appeared, no less important, no less exhilarating than clinical results. And it was, indeed, a fantastic venture for us to be among those who lived through what can be considered an actual biological and medical revolution.

The Offspring of Transplantation Research

From 1969 to 1973 I was a member of the WHO Advisory Committee on Medical Research. During each session, I had the uneasy feeling that the field of transplantation research was taboo. They just did not want to hear about it. In a world where malignancies and arteriosclerosis, infectious diseases, malaria and parasitoses, malnutrition and starvation killed millions of children and adults yearly, it was considered indecent to spend money on a type of research intended to improve expensive treatments restricted to a limited number of patients in rich countries.

I was, of course, sensitive to this attitude. After some time, however, I thought I might have found a good answer to propose, and when I was chosen for the WHO lecture given yearly by one member of the committee, I entitled my paper: "Transplantation Story, or How Transplantation Research Leads to Fields of Biology and Medicine Far Removed from Organ or Tissue Transplantation." In it I tried to show how recent progress in allograft immunology resulted in such advances in our medical and biological knowledge that it far transcended the mere problem of organ replacement.

The era of transplantation has produced the most fantastic change in the history of biology and medicine. The HLA story, the definition of personality, the importance of genetic polymorphism for species survival, the prediction of disease or at least of diseases to which one is exposed, the many secrets of cell-mediated immunology, the major role of new mediators such as cytokines, the importance of the recognition of the self for cell interactions, the more and more important field of autoimmune diseases: in brief, a hundred new approaches to the image of man and the cure of diseases - a true revolution will have resulted from a body of research which, at the beginning, had an apparently limited aim: to find a way of replacing a destroyed organ.

CURRICULUM VITAE

Jean Hamburger

PERSONAL

Born:	July 15, 1909; Paris, France
Nationality:	French
Home Address:	38 rue Mazarine 75006 Paris, France
Office Address:	Académie des Sciences 23 quai Conti 75006, Paris, France

EDUCATION

1930	University of Paris, Ph. D.
1936	Paris School of Medicine, M.D.

POSITIONS

1952-83	Hôpital Necker, Paris, Chief, Department of Nephrology
1952-83	Director of a Research Unit on nephrology and immunology, Institut National de la Santé et de la Recherche Médicale (INSERM) and Centre National de la Recherche Scientifique (CNRS)
1956-83	Professor of Medicine, Université René Descartes

PROFESSIONAL SOCIETIES

1960-63	President, International Society of Nephrology
1960-70	President, Transplantation Society
1947-	Founder and Vice-President, French "Fondation pour la recherche médicale"
1968-72	Member, Scientific Committee of the W.H.O.
1977-	Member, "Conseil de l'Ordre de la Légion d'Honneur"
1981-	President, "Palais de la Découverte" (French Science Museum in Paris)
1974-	Member, French Académie des Sciences
1975-	Member, French Académie de Médecine
1985-	Member, Académie Française
1990-	President, French Académie des Sciences

AWARDS

Honorary FACP (USA)

FRCP (Canada, London, Edinburgh)

Fellow of Royal Society of Medicine and other foreign societies (Argentine National Academy of Medicine, Mexican Academy of Medicine, Académie Royale de Belgique, Polish Academy of Sciences, etc.)

Doctor Honoris Causa of the Universities of Athens, Buenos Aires, Edinburgh, Geneva, Lund, Liège, Louvain, Montreal, and Porto

David Hume and John Peters Awards

Grand Officier de la Légion d'Honneur

Grand Officier de l'Ordre National du Merite

Commandeur de l'Ordre des Arts et Lettres

PUBLICATIONS

Many scientific books and twelve books for the general public (philosophy and literature) translated into English:

1968	Nephrology, 2 vol., W.B. Saunders
1971	Structure and Function of the Kidney, same publisher
1972	Renal Transplantation, Williams & Wilkins (2nd edition, 1981)
1973	The Power and the Frailty, Macmillan
1978	Discovering the Individual, Norton
1979	Nephrology, John Wiley
1971-90	A yearly series "Advances in Nephrology" coedited by Jean Hamburger, The Year Book publisher

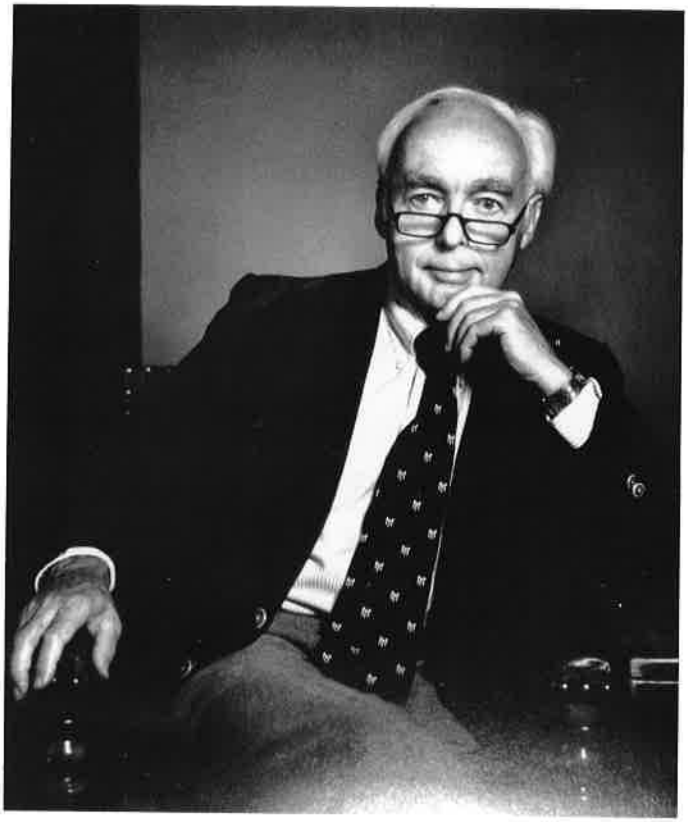
REMINISCENCES OF A "TRANSPLANTER"

Rupert E. Billingham

Address: Route 2, Box 102B
Vineyard, Haven, Massachusetts 02568

Rupert E. Billingham

1967



1988

REMINISCENCES OF A "TRANSPLANTER"[a]

Rupert E. Billingham

Frequently we are assailed by curiosity to know how a particular person has come to follow a particular career and start to develop his own distinctive research interests, teaching competence, or other professional skills. To the outsider, a scientist's professional development and achievements usually appear to have followed a reasonably logical pathway. Do they really reflect the faithful follow-through of a well-conceived master plan, formulated at a relatively early stage in his training, or has molding by chance or unpredictable events all along the line played an important, if not the major role? These possibilities, of course, are not mutually exclusive.

Retirement in 1986 marked completion of 40 years of "service" as a "transplantation biologist" or "transplanter," a period almost coeval with the explosive development of the subject. This chapter represents an attempt to identify or trace significant events that led to my entering this field, my own activities in it, and, eventually, to my leaving England in 1957 in favor of an academic life in the United States, which I was happily pursuing in the Department of Cell Biology at The University of Texas Southwestern Medical School at Dallas. Indeed, an appropriate subtitle for this essay might be: "From Oxford to Dallas."

Sailor to Graduate Student

In 1946, after unexpectedly fulfilling a boyhood desire to join the Royal Navy by four years' wartime service in antisubmarine escort vessels, I returned to the University of Oxford, where I had previously taken my bachelor's degree in zoology, hoping to be given the opportunity to "try my hand" at research. I received a warm welcome from each of my former teachers in the Zoology Department, as I visited them in turn to explore possible openings for a graduate student and to seek suggestions as to what I might do. All but one, very reasonably, asked me what I wanted to do (to which I had no very satisfactory answer). They gave me reprints of some of their contributions to scientific journals, which I had considerable difficulty understanding, and politely invited me to spend a few weeks in the library in search of a project of my own before returning to discuss it. As each visit produced an essentially similar response, my morale sank lower and lower. In retrospect, I consider this to have been the most worthless piece of well-intended advice I've ever received, and I've never given similar direction to anyone else, especially to one who has been totally away from the biological sciences for several years and has never done any research.

As a student I had always been interested in marine biology. During my Navy days it was a subject that kept me busy in my spare time, whether at sea (the ship's medical officer could usually be prevailed upon to lend his microscope) or ashore, and which got me into trouble on more than one occasion. For example, in April 1943 while we were escorting a westbound convoy a few hundred miles off the coast of Newfoundland in exceedingly bad weather, a strange looking fish was washed up over our forecastle and wedged in a hawsehole. At the time, being a supernumerary flotilla radar officer aboard HMS *Escapade*, I was slinging my hammock in the captain's sumptuous day cabin aft, which he seldom visited while we were at sea. What could be more natural for me than to place this large, rather rotund fish upon a tray on his desk in order to sketch and to dissect it? Alas, the pitching and rolling of the ship took the beast on many excursions in the cabin before my task was complete, and all was not well when the captain learned what I'd been doing from his servant and from my fellow officers, all of whom had displayed considerable interest in my project. I was summoned to the bridge, verbally torn apart, and from then on had far less attractive sleeping quarters!

---

[a] Slightly updated and revised version of an article of similar title by kind permission of the editor, Felix T. Rapaport M.D. and the Publishers, Grune and Stratton, *Transplantation Proceedings*, vol. 6, No. 4 (December 1974).

However, there was little prospect of my being able to further my interest in marine biology at Oxford because of its inland location, and I was beginning to feel very depressed about the possibility of finding a suitable, or feasible and worthwhile, research project. Then my luck changed. The last person for me to call on in the department was a junior faculty member named Peter Medawar, who had been one of our laboratory instructors five years previously and who, I had learned, was now regarded as a very bright though unconventional zoologist. Indeed, there were rumors abroad that he had rather wild ideas. Several graduate students warned me that I would be taking a great risk if I worked under his supervision!

At this time, as a member of an energetic research team headed up by Dr. John Z. Young, he had spent several years' War Work on the repair of peripheral nerve injuries, which involved the study of nerve autografts and homografts. Subsequently, Medawar performed his now classic experiments comparing the fate of skin autografts and homografts in rabbits and in man. He, too, gave me reprints to read, some of which had been written for laymen. They dealt with such topics as growth, senescence, biological individuality, and wound repair, which I could easily understand and found exciting. He told me about "pigment spread," an interesting phenomenon he'd just read about that occurred in the skins of spotted guinea pigs and that had been under sporadic study for nearly 50 years. Essentially it comprised the apparent slow encroachment of pigment from black into white skin areas, and the challenge was to account for this tinctorial transformation. Medawar thought it might be due to some kind of "infective" process, mediated by the serial propagation of some kind of self-replicating agent that is part of the normal equipment of cytogenetically black, melanin-producing cells into their non-melanin-producing homologs in white skin. He felt that work on this problem might afford some insight into how the different cell "races" of the body come to acquire and maintain their specificity of tissue type (1,2).

I accepted Medawar's invitation to collaborate with him in analyzing this phenomenon and so became a graduate student. I don't know whether he ever realized that he'd rescued a sailor from drowning in a sea of despair. My thesis title was "Coat Coloration in Mammals with Special Reference to the Problem of Pigment Invasion." It didn't take many weeks to obtain a supply of spotted guinea pigs and develop the simple grafting procedure needed to place black-skin autografts in white-skin host areas and vice versa to bring the phenomenon under experimental control.

I was delighted with the project - the immediately pertinent literature was negligible, and there were reasonable grounds to believe that there wasn't much competition in the field. What I did need to acquire was a good knowledge of the structure and biology of skin - a really fascinating task.

In the course of our work we made use of heterotopic skin grafts having different "phenotypic" or regionally distinctive properties, eg, thick, hairless, sole of foot skin, tongue skin, or exquisitely transparent corneal "skin," which we transplanted to hair-bearing regions of the trunk. These revealed how rigidly different kinds of skin conserve the specificity of their epidermal epithelia on grafting to anatomically unnatural sites and initiated in me a long-lasting, active interest in the origin and conservation of different epithelial specificities, ie, of epithelial-mesenchymal relationships. In this work, we also innovated the use, for both grafting and microscopic studies, of viable sheets of pure, superficial epidermis separated from its dermal substrate by means of trypsin. With the aid of such preparations we established that, in the guinea pig, melanocytes are a lineage of cells *sui generis* within the epidermis and are exclusively responsible for melanogenesis. Naturally, having established the structure and function of the melanocyte in guinea-pig epidermis, we wished to find out whether these almost completely overlooked or unrecognized cells were also constant ingredients of human epidermis. But how were we to get hold of the fresh specimens of human skin?

The late Dr. T. Pomfret Kilner, then Nuffield Professor of Plastic Surgery at Oxford, kindly came to our rescue and made me a welcome guest at his "table," properly scrubbed and gowned, of course, and with petri dish in hand, to receive the trimmings and "leftovers." Through his kindness I also learned what it was like to travel in a Rolls-Royce motor car. Unfortunately, at that time the only skin that Kilner could provide was from Caucasians, and ultimately we needed black skin. Fortunately, however, he remembered a London colleague who, he said, often had to deal with the aftermath of enthusiastic knife fights among seamen in the London dockland, and who he felt would be able to help us. Eventually a telegram summoned me to a Harley Street address. I was courteously received by a formally dressed consultant. "Here's your specimen of black skin," he said, producing and opening a small saline gauze package to reveal what was unmistakably a considerable proportion of deeply pigmented human scrotum. I commented that it was an unusual sample of skin. "Yes," he replied noncommittally, "the poor fellow must have shut himself in a door." I hurried this trophy back to the laboratory and presented it to Medawar who commented, "Revolting," and off to work we went to obtain the sheets of pure scrotal epidermis necessary to study the pigment cells. Apart from these, our preparations revealed the existence of an interesting contour pattern that the lower surface of scrotal epidermis presents to the subjacent dermis. Subsequent work has shown that unique, dermoepidermal interface patterns exist in many regions of the body - the microanatomy of the epidermis is a fascinating subject. Our unknown donor's memory is perpetuated by illustrations of his scrotal epidermis and melanocytes in at least three journals.

Thus, as a result of experiments in which I was using skin grafting to study cutaneous pigmentation and epidermal specificities, I became acquainted with both plastic surgeons and dermatologists and, not unnaturally, developed an interest in some of the basic problems in these areas of medicine. I also become aware of the virtual total lack of communication or of any mutual interest between these two specialties, both of which are heavily committed to the cutaneous system.

The Most Important Lecture I Ever Attended

In 1947 Medawar presented a joint paper on our work on pigment spread at an international symposium on growth in relation to differentiation and morphogenesis, which the Society of Experimental Biology held at Oxford. No manuscript had been prepared, and I hadn't the least idea how he would handle the considerable bulk of data, ideas, etc., we had accumulated during our first year's work. I was astounded by his masterly presentation and the compelling reasons he gave for our choice of problem. He presented a persuasive argument - one I would never have thought of - which clearly gripped everyone present, despite their highly diverse backgrounds in biology. I was surprised to find that his account of our experiments bore no relation to their actual chronology; some time-consuming efforts that came to nought were totally ignored. In the course of the investigation some experiments we'd carried out had little more than serendipity as their justification but had yielded interesting results and opened up new avenues of approach. However, I noticed that in the lecture, "chance" received no credit for its contributions - hindsight had enabled creditable reasons to be invented for the performance of these experiments.

As the story unfolded, it had a beautiful logical sequence, like the plot of a well-contrived detective story. Alternative hypotheses were put forward to account for particular observations and previously, as well as subsequently, conducted experiments were described as if specifically designed to discriminate between hypotheses. Indeed, as I recalled, some of these experiments had been done for quite different reasons.

The response of his audience left no doubt concerning Medawar's mastery of the art of presentation, as well as that of research - indeed, probably many of those present were unaware that two separate talents had been involved in his performance. It was obvious to me that the only items that were sacrosanct or inviolable in this lecture were actual factual observations. Hypotheses could be invented or rejected at will, and the chronology of the experiments conducted and the reasons for embarking upon them could be altered to make the best possible story - in effect to make the most economical and lucid presentation.

In a subsequent session of this symposium, the late Dr. J. H. Woodger gave what amounted to a lecture on scientific method. I was amused when he cited Medawar's contribution as a model of its kind, exemplifying how an investigation should be tackled. Obviously, it had never occurred to Woodger that Medawar's narrative represented a gross travesty of the true history of the project, despite the meticulous honesty with which observations were treated.

I have dwelt at length upon this particular experience since, in retrospect, I can see that it was an important educational event for me. It taught me that to realize one's full potential as a scientist, one must master two quite different arts: a) techniques and background knowledge pertinent to a particular problem or field of research, and b) the art of presentation, whether via the written or spoken word. Some talented scientists have never acquired the art of presentation, and, to all but the sophisticated, their contributions are colorless observations or speculations deprived of a story. On the other hand, some third-rate scientists have mastered the art of presentation so successfully that their shortcomings are rarely suspected - they should become politicians!

Oxford to Birmingham

In 1947, when I had scarcely completed my first year of research and things were going along very smoothly, I was confronted by a crisis not unknown in graduate education. My supervisor informed me that he had accepted another position - the Mason Chair of Zoology at the University of Birmingham. Should I forsake the ancient, mellowed stone milieu of the University of Oxford with its deep-rooted traditions, and life in the family home in the countryside (so pleasant after four years' cramped existence on board small ships), for a junior faculty position in a "red brick" university and life in a lodging house garret in an area of England deprived of charm by the Industrial Revolution? If I were interested in my work and my future there was only one possible decision. I went to Birmingham and found the University to be refreshingly liberal after the conservative stuffiness of

Oxford. There was much more collaboration between basic scientists and their colleagues in the medical school than I had noticed at Oxford. I spent four very happy years at Birmingham, working only a short distance from the site of William Withering's home.

Apart from being highly productive research years, these were years during which the main themes of my subsequent scientific interests and activities developed, as we shall see. We continued our work on pigment spread, during the course of which we noted that, contrary to expectation, by transfer of *low* dosages of melanocyte-containing epidermal cell suspensions, pigment formation could be initiated in genetically alien hosts and not infrequently serially propagated through several hosts. I also became interested in various problems of wound healing as it related to the skin. Dr. Joyce Reynolds and I studied the possible use of viable suspensions of epidermal cells as a means of procuring the prompt re-epithelialization of massive, full-thickness cutaneous lesions in rabbits. At the time we were enthusiastic about the relevance of our work to the treatment of extensive burn injuries.

In 1950, when the early exciting pioneer work on ACTH and adrenal corticosteroid hormones was being carried out in the United States, we obtained a limited supply of these to study their influence on the rabbit's capacity to reject skin allografts. Collaborative experiments (3) with Medawar and P. L. Krohn got me directly and heavily involved in transplantation immunology for the first time. How delighted we were to find that both systemically and topically administered cortisone acetate was highly effective in weakening a rabbit's capacity to reject allografts - one of the first pieces of evidence that indicated that the homograft reaction was susceptible to interference. We had many discussions with clinical colleagues about the possibility of using this hormone to extend the useful life span of skin allografts on badly burned children (the nearby Birmingham Accident Hospital had an excellent Burns Unit under the directorship of Dr. Leonard Colebrook).

At this same time, Dr. Alan S. Parkes and his colleagues at the National Institute for Medical Research at Mill Hill, London, reported their accidental discovery of the capacity of dilute solutions of glycerol to protect chicken spermatozoa against the otherwise adverse effects of freezing and thawing. We found that this remarkable cryoprotective effect of glycerol extended to skin grafts and to epidermal cell suspensions prepared therefrom. Indeed, we successfully stored rabbit skin for many months at -79°C after its impregnation with 15 percent glycerol (4). Also in this dawning era of modern cryobiology came a provocative report from Dr. W. E. Gye and others at the Imperial Cancer Research Fund's laboratories in London that certain lyophilized tumors of mice, which were "dry as dust," generated new tumors on rehydration and inoculation into compatible hosts. Gye interpreted the latter as having arisen through transformation of host cells by an oncogenic virus rather than to the presence of viable tumor cells in the inocula. Prompted by this work we studied the capacity of skin to retain its viability after desiccation from the frozen state, following impregnation with dilute glycerol. Reduction of the normal water content of about 70 percent to 25 percent proved to be compatible with viability.

A Visit to the Promised Land

My first visit to the United States (of approximately three weeks' duration) came in the fall of 1950 in response to an invitation to talk about pigment spread at an International Congress of Cell Biology held at Yale. I spent 10 days crossing the Atlantic on the old S.S. *Georgic* and about a week getting home on the *Mauretania*. At the conference I recall meeting two great emeritus professors of American biology, Ross G. Harrison and Warren Lewis, and a dynamic contemporary biologist, Paul Weiss, who very kindly tried to persuade me to prolong my stay and work in his department at Chicago for a year. I became acquainted with many young people in my own age group at this conference; Clifford Grobstein, J. P. Trinkaus, Morris Foster, Herman Chase, and others destined to become leaders of American biology. In a visit to the Rockefeller University, I had the privilege of meeting Dr. Peyton Rous and Dr. Keith Porter.

A Cattle Story

In 1949, Medawar attended a microbiological congress in Sweden and, as I understand it, over a cocktail met with a geneticist from Scotland, Dr. H. P. Donald, Director of the Agricultural Research Council's Animal Breeding and Genetics Research Organization. Dr. Donald was struggling with the problem of distinguishing between monozygotic and dizygotic twins in cattle, using the conventional methods of phenotypic appraisal. Medawar offered to help out in the confident and perfectly reasonable expectation that exchange of skin grafts would afford the basis of an unequivocal test for monozygosity as it had previously done in a celebrated medicolegal case in Switzerland.

The acceptance of this offer introduced us both to cattle and their progeny at Cold Norton Farm, located in Staffordshire, some two hours' drive from Birmingham. The farm was totally devoid of any surgical facilities but liberally endowed with mud and excrement. Its redeeming features were plenty of intractable experimental subjects and willing, highly skilled colleagues who knew how to handle them. I recall phoning my dentist just before the first grafting session to seek his advise about a potent local anesthetic that would enable us to remove small skin grafts from the ears of cows, calves, and occasionally bulls without antagonizing them too much.

It didn't take us long to develop a relatively simple and reliable grafting technique applicable to these animals and to discover that they rejected skin allografts just as promptly as other species. The majority of alleged monozygotic twins did, in fact, accept each other's grafts as anticipated, but, to our chagrin, grafts exchanged between putative dizygotic twins, including members of some bisexual pairs, were usually accepted as well. We noted that the tolerance displayed by such animals to grafts from their co-twins did not extend to grafts from full siblings of separate birth or from their parents.

One day, as we were leaving the farm, troubled by confirmation of the mutual acceptance of each other's grafts by unequivocal dizygotic twins, ie, those of dissimilar sex, which we were completely at a loss to explain, we met Dr. Donald and briefed him on the status of the project. He advised us to go home and read "Immunogenetic Consequences of Vascular Anastomoses Established between Bovine Twins," a 1945 paper by Ray D. Owen published in *Science* which he felt might help resolve our problem. This paper revealed that dissimilar twins in cattle are permanently chimeric with regard to their erythrocytes, presumably as a result of mutual prenatal exchange of hematopoietic stem cells.

It is interesting to recall that in 1949, F. M. Burnet and F. Fenner had published a short classic monograph, "The Production of Antibodies." They presented an important theory about the means by which antibody-forming cells come to distinguish native from foreign molecules, ie, make the important distinction between "self" and "non-self". Mainly on the basis of Owen's work, they made the important prediction that if embryos or very young animals were to be exposed to antigenic substances, then when they grow up, their power to react against those substances would be abolished or at least impaired, ie, a state of specific immunological tolerance would result. Once we had read Owen's paper, the cattle work became an analysis of nature's experiment on the induction of immunological tolerance, carried out on a rather unamenable species (5).

Just as the work began to get exciting, it suffered a setback. We were speeding out to the farm along a main highway when a trash cart suddenly emerged from a sideturning; a crash was inevitable. I recall "coming to" in the middle of the road amid a pile of spilled garbage. Fortunately an ambulance had been following us, and promptly we were invited aboard and taken to a local hospital where a few stitches put us shakily back into circulation. Subsequently, we played the witness role at a police court where a charge of dangerous driving was brought against the driver of the trash cart. It was my first court experience, and I well recall the incident for two reasons: the driver's mate proved to be illiterate and suffered the indignity of having to repeat the oath word for word, after a policewoman; secondly, after aggressively cross-examining Medawar trying to discredit his version of the incident for the benefit of his client, the defense lawyer suggested to the magistrates that professors were probably as notoriously absentminded in driving as in other affairs. He gave me a hard time too. When we were leaving the court this lawyer unexpectedly approached us with a friendly demeanor, shook hands like an old friend, and offered his services any time we were in trouble. What an actor he'd been!

During one of our visits to inspect our cattle, I recall being invited into a barn to watch a veterinarian artificially inseminate a cow. On witnessing this far from wholesome procedure from a distance, I gained the erroneous impression that, at least on this occasion, the semen had been introduced into the wrong lumen, for clearly the vet had one arm up to the elbow in the poor beast's rectum.

At the time this work was in progress, meat was still severely rationed in postwar Britain. Thus, for both scientific and *other* reasons, we looked forward to the killing of some female calves born co-twin with males, and whose grafts they had totally failed to reject, to establish their freemartin status on an anatomical basis. Alas, when we arrived at the farm we found that the "execution" party included, in addition to a local butcher, a Ministry of Food inspector whose job it was to ensure that all the resultant meat went through the approved channels. When the whole gory business was concluded, I was offered some lungs which I politely declined on the grounds that I had no pets to feed. Not until a few years later did one of my former agricultural colleagues confide to me that after we'd left the farm that day, there *had* been a share-out of some more-tasty cuts - they excluded us from this division of the spoils because academics were considered poor risks as law violators or black marketeers.

Birmingham to London

After four years at Birmingham I accompanied Medawar again when he moved to University College, London, to the prestigious Jodrell Chair of Zoology and Comparative Anatomy. "Thank God we've left those cows behind," he said. At University College, in collaboration with Leslie Brent (now Professor Emeritus of Immunology at St. Mary's Hospital Medical School, London), we set ourselves the task of trying to experimentally reproduce the graft tolerance situation in mice and chickens that occurs naturally in genetically dissimilar cattle of multiple birth (6).

With the chickens, we spent a lot of time injecting blood from adult donors intravenously into embryos hoping to hatch them and subsequently test their capacity to reject skin grafts from their respective blood donors. A very high percentage of the embryos died a few days after inoculation, and at the time we attributed their demise to the presence of pathogenic microorganisms introduced along with the adult blood. The few survivors we obtained proved to be tolerant of their test grafts, as did chicks that had been injected in ovo with blood from embryo donors. Indeed, embryos' blood was perfectly harmless.

Twin Chicks Go to College

The twin embryos that develop in double-yolked eggs are dizygotic, and it was easy to establish the existence of vascular intercommunications between the blood circulations of these natural parabiont organisms. We therefore set ourselves the task of determining whether, when such twins hatch, they are chimeric with regard to their blood and also mutually tolerant of each other's skin grafts. Unfortunately, successfully hatching both chicks from a double-yolked egg is a very rare event, and we only managed to raise a few pairs out of the considerable number of double-yolked eggs incubated - sufficient, however, to confirm our prediction.

Before we managed to raise a pair of twin chicks, our attention was drawn to a newspaper report of a poultry farmer who was successfully rearing a pair of twin chicks. Through the cooperation of the press the farmer was traced; he sold us, at a considerable sum, I believe, his twins "for the good of science." "Twin Chicks Go To College" became the news headline. We gave these animals royal treatment, and when they were a few weeks old, we exchanged skin grafts between them - these were rejected with normal promptitude! In the light of our various findings we have always suspected that one of the original twins must have died, and to "save face" a surreptitious substitution had been made. Little did the presumed felon realize the discriminating power of transplant immunology.

While this work was in progress, Dr. Alex Comfort, a colleague who had recently taught himself Russian, drew our attention to and kindly translated for us a paper in that language by a Czech biologist, the late Dr. Milan Hašek. He had devised a simple and extremely elegant procedure for placing chick embryos in experimental synchorial parabiotic union so that vascular anastomoses develop. With the aid of this technique we were soon able to produce pairs of chickens that were erythrocyte chimeras and mutually unresponsive to each other's skin grafts.

We were also trying to induce tolerance of skin homografts in mice by inoculating in utero the fetuses of mice of one inbred strain with viable cell suspensions prepared from a variety of tissues of adult donor mice of an unrelated strain. This procedure was bedeviled with abortions, and the mauling or eating of newborn litters by their mothers. We did manage to raise sufficient intra-embryonically inoculated mice to establish that tolerance of skin allografts could be induced in this species, but the logistics of obtaining all the tolerant mice we needed for extensive experimental purposes were too exacting.

An Unpublished Study on Wound Healing

Peter Medawar came into my laboratory at University College late one afternoon, looking rather shaky and clasping a blood-soaked gauze pad around a finger. "I've just had an accident cleaning a test tube," he said, inviting me to come into his laboratory where he had put everything ready for me to sew him up. I examined the wound and was concerned about its depth and the anatomical structures revealed. He had provided the finest eyeless suture needles available for my use - the type we used to sew up mice. The first three needles absolutely refused to penetrate his skin and immediately bent out of shape. But what really bothered me was Peter's evident discomfort and pallid appearance. I feared that he might collapse on me. I can't tell you how relieved I was when, a few days later, he showed me the result of this never-published collaborative work on wound healing.

America Revisited

In June 1955, I attended a symposium of the Society for the Study of Development and Growth on the beautiful Amherst campus (this time I flew the Atlantic), and the visit was to have a considerable impact on my future research activities. At this relatively small meeting I had the good fortune to meet and become acquainted with many leading developmental biologists, in particular a delightful young mammalian geneticist, Dr. Willys K. Silvers, a fellow pigment-cell worker.

Apart from the eminence of the majority of the participants at this meeting, which was superbly organized and ultimately led to a most useful publication, two things impressed (or horrified) me: first, many speakers made little use of notes or the clock. They rambled on and on, so that a two-hour talk was not unusual - the record was two-and-a-half-hours! Secondly, all too frequently the presentations were primarily directed at the "in" groups, so that I, at any rate, had a hard time following and often felt a complete moron. I've often wondered how many of my fellow conferees also suffered out this marathon! Alas, when a meeting is small and you are an invited participant with all expenses generously paid, you can't very well play hooky without offending your host.

I have never been a very careful planner or diary keeper, so that chance rather than careful calculation is the only protection I have to preclude my being confronted by the fulfillment of mutually conflicting commitments. I recall that when I received the invitation to participate in the Amherst meeting, my wife, who was pregnant at the time, drew my attention to the fact that the expected time of arrival of our second child would be right in the middle of the conference. She very nobly urged me to accept. Immediately after my presentation at the symposium, Dr. James Ebert, the session Chairman, warmly congratulated me on the birth of a son and read a telegram aloud that had been handed to him while I was speaking.

After the meeting, Dr. Robert Briggs drove me to Philadelphia to visit the Institute for Cancer Research. I was greatly impressed by all I saw and was honored when offered an attractive position by the Director, Dr. Stanley Reiman. However, discomfort because of the hot, humid weather to which I was unaccustomed, compounded by the thick English suit I was wearing, made me decide that I couldn't possibly live in such a climate. One simple event made this trip extremely rewarding: in Dr. Briggs' laboratory I saw some exceedingly fine (30-gauge) syringe needles, about 0.3 mm in external diameter, with which I felt sure it would be possible to perform intravenous injections on newborn mice. Because of the success that had attended our attempts to induce tolerance of skin grafts in chickens by neonatal intravenous injections of adult donor blood, Brent and I felt that this might be feasible in the newborn mouse, too. Perhaps I was too modest in my approach, but tactful hints about what we might be able to achieve with the aid of the fine needles I saw failed to procure a gift sample. I couldn't get back to London soon enough where happily we were able to get some of these needles specially made. A few afternoons' work established the feasibility of intravenous injections of up to 0.1 ml of saline via the orbital branch of the anterior facial vein or the sagittal sinus of the newborn mouse. A more formidable problem to be solved was preparing suspensions of viable splenic or other tissue cells that would not cause fatal emboli.

Early in 1956, the Royal Society of London under the leadership of Sir Macfarlane Burnet (7), sponsored an international discussion meeting on tolerance. It was the first meeting specifically devoted to this new facet of immunology, and it afforded me the opportunity of becoming acquainted with the founding members of the "cult." By this time, we hadn't progressed very far with the induction of tolerance by intravenous injection of newborn mice. All we had to show for our trouble were two healthy A-strain mice, which, as a result of intravenous inoculation with splenic cells from an adult CBA-strain donor on the day of birth, bore healthy CBA-strain test skin allografts of about 16 days' standing with short fur crops (grafts on untreated control hosts are normally rejected within 11 days). On this rather dubious basis, we decided to commit ourselves *totus porcus*. In a joint paper, Brent described our technique for the intravenous inoculation of newborn mice and stated that 100 percent of the survivors (two of two) had been rendered tolerant - facetiously he commented that only a statistician would require better proof than this. Sir Ronald Fischer evidently felt dissatisfied, since, rather ostentatiously, he got up and walked out. Needless to say, within the next few weeks experimental results amply confirmed our extrapolation. Anyone with some inbred strains of mice, some 30-gauge needles, and a few simple instruments could now abrogate the homograft reaction at will by producing tolerant animals in large numbers.

With some of the mouse strain combinations that Brent and I were using in our tolerance-induction experiments, many, if not all, of our inoculated subjects subsequently developed and often succumbed to a mysterious wasting syndrome that we dubbed "runt disease" (8). This was the second time in our tolerance work that intravenous inoculation of viable cellular components of an adult donor's lymphohematopoietic tissue system caused the deaths of allogeneic immature hosts. The first experience was when we found that nearly all avian embryos inoculated with *adult* chicken blood died *in ovo*. Happily, on second encounter, we immediately suspected that the disease was the result of reactivity on the part of the inoculated immunologically competent cells or immunocytes against their immunogenetically alien hosts, ie, graft-versus-host reactivity. We soon succeeded in confirming this, and graft-versus-host reactions in mice, rats, hamsters, rabbits, and guinea pigs have been a rewarding subject for investigation in my laboratory ever since (9).

In 1954, Dr. Paul Russell, a surgical resident from the Massachusetts General Hospital (now John Homans Professor of Surgery at Harvard University), joined us for a year. We spent a lot of time together, studying the phenomenon of wound contracture as it is expressed in extensive full-thickness cutaneous lesions in rabbits' skin (10). We found the subject very interesting but were horrified by the inescapable fact that our data had to be subjected to statistical evaluation, ie, *mathematics*, a subject for which I have never been able to summon either aptitude or interest. In studying the reepithelialization of extensive granulating wounds, we noted the neogenesis of hair follicles previously reported by Breedis - a phenomenon that encourages us to believe in the ultimate feasibility of procuring cutaneous neogenesis for therapeutic purposes. A year or two later, this led me to study a natural example of cutaneous neogenesis that occurs in association with the growth of antlers in deer.

Through Paul, I learned quite a bit of experimental surgery, which has served me in good stead, and equally important, I believe, I learned a great deal from him about science and medicine in the United States.

Paul returned to Boston in 1956 to complete his surgical training, and William Hildemann, who had recently earned his Ph.D. with Dr. Ray D. Owen at Cal Tech, joined us. For some while I had been studying the literature on tumor transplantation in Syrian hamsters, from which it appeared that for some reason or other, allografts were invariably accepted in this species, whether they were implanted in the tissue forming the highly vascular walls of the cheek pouches or elsewhere. We suspected that the known unitary origin of all domestic hamsters (from one male and two female littermates unearthed from a burrow in Aleppo, Syria, in 1930) might have been responsible for the apparent hospitality that these animals extended to allografts. Bill Hildemann and I succeeded in obtaining breeding nuclei of some long-closed and partially inbred strains of hamsters in London and found that with some donor-host combinations, hamsters can reject skin allografts with normal promptitude (11). We subsequently inbred these and other hamster strains for genetic studies. Collaborative studies with various colleagues, and later their own independent work, established the hamster as an extremely valuable experimental subject for transplantation immunology work. Findings that have emerged include: the paucity of segregating histocompatibility genes in domestically available hamsters; the immunologically privileged status of the cheek pouch as a graft site (Dr. Clyde F. Barker); the hamster's ability to express transplantation immunity as a striking delayed-type, cutaneous hypersensitivity reaction like the classical tuberculin reaction in man and the guinea pig; and the "irradiated hamster" test for histocompatibility in man developed by Dr. H. Ramseier and Dr. J. W. Streilein.

Like John Hunter, I had once tried, unsuccessfully, to freeze and revive fish. Aware that Hildemann was an authority on the biology of fish, I sought his help with the problem. We exposed some small goldfish to slowly increasing concentrations of glycerol in the hope that they would absorb enough of it across their gills to afford them cryoprotection. Alas, to our chagrin exposure to this reagent caused profound locomotor disturbances which Medawar facetiously suggested might be due to the inebriating influence of glycerol, a trihydric alcohol. Needless to say, this experiment was a total failure, even when dimethylsulfoxide was substituted for glycerol.

Emigration

Toward the end of 1956 I received a visit in my London laboratory from Dr. Hilary Koprowski, then of the viral and rickettsial section of Lederle Laboratories, whom I knew quite well because of his interest in tolerance. He informed me that he had recently accepted the position of Director of the Wistar Institute of Anatomy and Biology in Philadelphia and offered me a generously salaried position to build up a transplantation research group there. Since a five-year Cancer Research Fellowship which then sustained me was about to enter its terminal year, a verbally transmitted invitation to take an attractive position at the Australian National University at Canberra remained unsubstantiated, and no alternative sources of employment had presented themselves, I accepted this offer. I wrote to Dr. Willys K. Silvers at the Jackson Laboratory at Bar Harbor almost immediately, inviting him to join me.

Thus, it came about that early in October of 1957 Will and I embarked upon what proved to be 14 years of productive collaborative work on many topics (12). I shall never forget my first day at Wistar, and particularly how depressed I felt for a long time about the prospects of getting much research under way. The Institute was largely a gloomy museum, totally devoid of decent laboratories and equipment and provided with direct current rather than alternating current in many places. The only assets we discovered were a fairly good animal colony with vast numbers of rats of a variety of partially inbred and generally ill-defined strains, including the "Wistar"! These had been bred and sold as a source of revenue. Certainly I would never have accepted this position had I been able to look at the place first, though I think the challenge to transform what was little more than an anatomical museum with ancillary bone collections, a collection of pickled fetuses with horrific congenital abnormalities (which intrigued my children), and a collection of brains from distinguished men, into an effective modern research institute, brought out the best in all of us.

I won't go into details about our research activities during the eight years I was at Wistar. Initially we inbred several of the available rat stocks and subsequently used them extensively for tolerance and graft-versus-host disease studies. Through this work, BN and Lewis rats have become familiar to most transplanters. Similarly, we developed and distributed MHA, CB, and LSH syngeneic hamster strains from closed colony stocks that I had brought from London.

By this time, I suppose, I came to believe that I'd learned about as much as I ever would about the art of being a scientist, until a new experience disillusioned me. I received an invitation to give the American College of Physicians' Alvarenga Lecture at exactly one-month's notice, and the title had to be submitted within 24 hours. Should I play it safe and talk about transplantation, or should I try and prepare something different? I decided to take a chance and selected "The Maternal-Fetal Relationship from the Viewpoint of Transplantation" as my subject (13). Of course the task I'd set myself was to consider the fetus as a successful allograft and review the evidence pertaining to its almost unqualified success. Preparation of this lecture took me into much new territory, which included reproductive biology, about which I knew but little; and I had to go more than thigh deep into problems of Ob-Gyn and learn about choriocarcinoma, moles, ectopic pregnancy, and the like, but it was rewarding since this particular field of immunobiology had been almost totally neglected. I had to publish the manuscript in the *Transactions and Studies of the College of Physicians of Philadelphia*. Six people (one from Norway) requested reprints. With appropriate permissions, I published a slightly modified version of the paper in the *New England Journal of Medicine* and was besieged by reprint requests. Out of one month's intense work in the library and in my study, and drawing very little on my own original work, came many fringe benefits, including conference trips to the Philippines, England, and Israel as well as many invitations to give seminars. Most important was the awakened desire in me to become an active research worker in this area. This was realized in 1967 when Dr. Alan Beer interrupted his residency training in Ob-Gyn at the University of Pennsylvania to spend a postdoctoral year working with me, and Alan and I worked together for at least 10 years. Indeed, the immunobiology of mammalian reproduction became my principal research interest (14).

After seven years at Wistar I was beginning to yearn for the more liberal academic life afforded by a university, with more exposure to students. I found medical schools particularly attractive because of my relevant interests. By chance, in 1964 I was participating in an American Cancer Society workshop on "The Epidemiology of Cancer" at Rye, New York. Among my fellow conferees was a senior member of the School of Veterinary Medicine faculty at Penn, Dr. Robert Marshak. In the course of conversation I happened to mention that I was dissatisfied with my present position and was seriously considering an offer I'd received from Johns Hopkins. Within a day or two I was called to the office of the Dean of the Medical School at Penn, Dr. Samuel Gurin, who gave me a warm welcome, asked if it were true that I was looking for another job, and told me that he would find something so attractive that I wouldn't want to leave. Thanks to the cooperative efforts of the Vice-President for Medical Affairs, Dr. I. S. Ravdin, provost David R. Goddard, and Dean Gurin, my fate was sealed in a pleasant and entirely acceptable manner.

In July 1965, a minor exodus occurred - my entire transplantation group, including technicians, walked across the street from Wistar to the University of Pennsylvania Medical School to initiate the new department and Henry Phipps Institute of Medical Genetics, where I spent six very happy years as Professor and Chairman.

From Philadelphia to Dallas

What persuaded me to move to Texas? I first visited Southwestern Medical School at Dallas early in 1958 to participate in a symposium on immunity and resistance to infection in early infancy. At this time I was greatly impressed by the excellence of the nearly new buildings. I can also recall having flown down as an NIH consultant on another occasion in the summer when, on stepping off the plane, I felt that I was being baked alive, the weather was so hot. In 1970, a faculty member informally solicited my interest in the chairmanship of a new Department of Cell Biology being constructed, but I told him that I was perfectly happy with my present position, besides which the Texas climate was too hot. However, a very energetic search committee chairman, whom I'd never met, subsequently maintained polite and persistent telephone contact with me over a five-month period, and eventually I consented to visit Dallas as a "consultant," present a seminar, and hopefully and politely get him "off my back." So disinterested was I in making this trip that I don't recall having done any homework for my seminar (no honorarium had been offered). I prepared it on the plane going down. Nor did I mention to my wife why I was going to Dallas. It seemed pointless. However, from the moment I arrived at Southwestern I was intrigued by all I saw and especially by a very evident esprit de corps that paid no heed to departmental frontiers, or the usually more formidable ones that separate so-called basic sciences from clinical departments in most medical schools. Sleep eluded me after I had been sumptuously dined and wined at the Old Warsaw with Dr. Donald Seldin as host on the first evening of my visit. At first I blamed the liquor, but no, the answer was clear - I had been "hooked." I was ready to be seduced by an offer of a job - needless to say the seduction did occur! I well recall arriving back in my home in Pennsylvania on a Saturday afternoon, euphoric after a champagne flight, and finding my wife signing the check to pay for a new roof that had just been put on our house. "We don't need it," I commented, "we shall probably be moving to Texas." This was the second time in my life I've had a house reroofed, and each time completion of the work has been associated with a change of jobs. We made quite sure that the home we chose in Dallas had a very sound, almost new roof!

For 40 years, chance has certainly been very good to me, but only rarely do I admit it. As a scientist, I'm a serendipitist; this again is something one should not admit to, especially when preparing grant applications.

ACKNOWLEDGMENT

This essay is dedicated with gratitude to all who have generously shared their knowledge with me, and above all to those who have pooled their skills with mine in the pursuit of that fascinating subject, transplantation biology. I am indebted to the British Empire Cancer Campaign and the National Institutes of Health, whose generous support has helped defray the expenses of our research activities.

REFERENCES

1. Billingham R, Medawar P. Pigment spread and cell heredity in guinea pigs' skin. Heredity 1948; 2:29.

2. Billingham R, Medawar P. Pigment spread in mammalian skin; serial propagation and immunity reactions. Heredity 1950; 4:141.

3. Billingham R, Krohn P, Medawar P. Effect of cortisone on the survival of skin homografts in rabbits. Br Med J 1951; 1:1157.

4. Billingham R, Medawar P. The freezing, drying, and storage of mammalian skin. J Exp Biol 1952; 29:454.

5. Billingham R, Lampkin G, Medawar P, et al. Tolerance of homografts, twin diagnosis, and the freemartin condition in cattle. Heredity 1952; 6:201.

6. Billingham R, Brent L, Medawar P. Quantitative studies on tissue transplantation immunity. III. Actively acquired tolerance. Philos Trans R Soc Lond (Biol) 1956; 239:357.

7. Burnet M. A discussion on immunological tolerance. Proc R Soc Lond (Biol) 1956; 146:1.

8. Billingham R, Brent L. Quantitative studies on transplantation immunity. IV. Induction of tolerance in newborn mice and studies on the phenomenon of runt disease. Philos Trans R Soc Lond (Biol) 1956; 242:439.

9. Billingham R, Defendi V, Silvers W, et al. Quantitative studies on the induction of tolerance of skin homografts and on runt disease in neonatal rats. J Natl Cancer Inst 1962; 28:365.

10. Billingham R, Russell P. Studies on wound healing with special reference to the phenomenon of contracture in experimental wounds in rabbits' skin. Ann Surg 1956; 144:961.

11. Billingham R, Hildemann W. Studies on the immunologic responses of hamsters to skin homografts. Proc R Soc London (Biol) 1958; 148:216.

12. Billingham R, Silvers W. The immunobiology of Transplantation. Prentice Hall, Inc., Englewood Cliffs, New Jersey, 1971.

13. Billingham R. Transplantation immunity and the maternal-fetal relation. N Engl J Med 1964; 270:667.

14. Beer A, Billingham R. The Immunobiology of Mammalian Reproduction. Prentice Hall, Inc., Englewood Cliffs, New Jersey, 1976.

CURRICULUM VITAE

Rupert E. Billingham

PERSONAL

Born:	October 15, 1921; Warminster in the County of Wiltshire, England
Marital Status:	Married; 3 children
Home Address:	Route 2, Box 102B Vineyard, Haven, MA 02568

EDUCATION

1943	University of Oxford, Zoology B.A.
1947	University of Oxford, Zoology M.A.
1950	University of Oxford, Zoology Ph. D.
1957	University of Oxford, Zoology, D. Sc.

MILITARY SERVICE

1942-46	Lieutenant in Royal Navy, served in anti-submarine escort vessels in Western Approaches Command and on East Indies Station

POSITIONS

1947-51	Lecturer in Department of Zoology, University of Birmingham, England
1951-57	Research Fellow of the British Empire Cancer Campaign; Honorary Research Associate, Department of Zoology, University College, London
1957-65	Member of Wistar Institute of Anatomy and Biology, Philadelphia, PA
1958-71	Professor of Zoology, University of Pennsylvania
1965-71	Professor and Chairman, Department of Medical Genetics, and Director of the Henry Phipps Institute, University of Pennsylvania School of Medicine
1971-86	Professor and Chairman, Department of Cell Biology and Anatomy, The University of Texas Health Science Center at Dallas, Southwestern Medical School
1986	Retired
1990-	Professor Emeritus of Cell Biology and Neuroscience at the University of Texas Southwestern Medical Center

PROFESSIONAL SOCIETIES

Royal Society, London
American Association of Immunologists
Society for Developmental Biology
New York Academy of Sciences
Society for Investigative Dermatology

Transplantation Society
1974-76 President

American Association of Anatomists

American Academy of Arts and Sciences

American Fertility Society

AWARDS

1940	Oxford Municipal Charities Exhibition
1950	Junior Research Fellowship of the British Empire Cancer Campaign
1953	Intermediate Research Fellowship of the British Empire Cancer Campaign
1961	Elected Fellow of the Royal Society, London
1962	Fellow of the New York Academy of Sciences
1963	Alvarenga Prize, College of Physicians of Philadelphia
1964	Honorary Award, American Association of Plastic Surgeons
1965	Honoris causa, Trinity College, Hartford, D. Sc.
1965	Elected Fellow of American Academy of Arts and Sciences
1966	Harvey Lecture
1967	Honorary Member, Society for Investigative Dermatology
1971	Frederick Lyman Adair Award, American Gynecological Society
1974	AOA, Honor Medical Society
1979	Kinyoun Lecture, National Institute of Allergy and Infectious Diseases
1981	Membre d'Honneur, Societe Francaises D'Immunologie
1981	Outstanding Teaching and Concern for Students Award, University of Texas Southwestern Medical College
1982	Distinguished Guest Lecturer, Society for Gynecologic Investigation
1983	Outstanding Faculty Award for excellence in teaching of the Freshman Class 1982-83, The University of Texas Health Science Center at Dallas
1988	Honorary Member, British Transplantation Society

EDITORIAL BOARDS AND EDITORSHIPS

1958-60	Transplantation Bulletin
1963-80	Journal of Experimental Medicine
1964-72	Journal of Immunology
1964-65/1976-80	Journal of Experimental Zoology
1968-72	Journal of Investigative Dermatology
1970-87	Cellular Immunology
1974-75	Immunogenetics
1980-	American Journal of Reproductive Immunology
1980-85	Placenta
1980-82	Transplantation

CONSULTANT AND ADVISORY COMMITTEES

1959-62	Member, Allergy and Immunology Study Section, National Institute of Allergy and Infectious Diseases
1968-70	Member, Transplantation and Immunology Committee, National Institute of Allergy and Infectious Diseases
1971-73	Chairman, Transplantation and Immunology Committee, National Institute of Allergy and Infectious Diseases
1965-70	Member, Scientific Advisory Board, St. Jude Children's Research Hospital, Memphis, Tennessee (Chairman, 1969-70)
1968-70	Member, Scientific Advisory Board, Medical Division Oak Ridge Associated Universities (ORAU)
1974-76	President, Transplantation Society
1976-79	Member, Scientific Advisory Committee, Massachusetts General Hospital
1980-83	Member, National Allergy and Infectious Diseases Council National Institutes of Health
1981-83	Sigma Xi College of National Lecturers
1983-86	President, International Society for Immunology of Reproduction

LISTED IN

American Men and Women in Science
Who's Who in America
World Who's Who in Science
The International Who's Who
Directory of British Scientists
Who's Who of British Scientists
Who's Who
Dictionary of International Biography
American Men and Women in Science, the Medical Sciences
The Blue Book - Leaders of the English Speaking World

RESEARCH INTERESTS

The biology of skin, with particular reference to its pigmentation and differentiation

The biology and immunology of tissue transplantation

The immunobiology of mammalian reproduction

Preservation of tissues and organs for grafting

Wound healing and regeneration

TOLERANCE AND GVHD: AN EXCITING DECADE

Leslie Brent

Address: St. Mary's Hospital and Medical School
Department of Immunology
Paddington, London W2 1PG
England

Outside Dept. of Zoology,
University College, London, 1954.

Leslie Brent

L. Brent climbing Mt. Snowdon, Wales, 1985.

L. Brent walking in W. Cork, Eire, 1986.

TOLERANCE AND GVHD: AN EXCITING DECADE

Leslie Brent

Introduction

I was somewhat dismayed when I first received Paul Terasaki's letter inviting me, as a "pioneer of transplantation," to contribute to this monograph. Flattering as it was to be thus described (scientists are almost as vulnerable to flattery as actors and politicians, and I am not at all exceptional in this regard), I have tended to reserve the word "pioneer" for men and women in their dotage who, in a bygone era, have made world-shattering discoveries that opened up, and illuminated, new vistas. The Curies, Pasteur, and Ehrlich come to mind, but the Oxford dictionary takes a more prosaic view: having begun with somewhat poetical, if military, definitions, it finishes up with "an original investigator, explorer etc; an initiator." That would seem to encompass all innovative scientists, including me, I suppose.

The second cause of my dismay, if I can call it that, was connected with the fact that a few months ago I entered into a contract with Academic Press to write *A History of Transplantation Immunology*. By hatching out this entrepreneurial volume of "Recollections" in addition to his already published volume on *History of HLA*, Paul seemed to have upstaged me and made my own contribution somewhat problematical. On further reflection this is clearly not so, and the two volumes edited by Paul may well prove useful to me as I write my more objective "History." These two quite different approaches will thus be complementary, and what I have recounted here are purely personal recollections that make no pretense at objectivity. I hope, nevertheless, to avoid the potential pitfall of exaggerating my own contribution and to give due credit to others, especially to Peter Medawar and Rupert Billingham.

R.E. Billingham with L. Brent at the Medawar Memorial Symposium, London (N.A. Mitchison in background)

My Entry into Science

Having spent over four years in the British Army and having secured a grant from the Ministry of Education, I was released in the summer of 1947 to enable me to commence my studies in zoology at the University of Birmingham. The head of the department was Peter B. Medawar, and one of the demonstrators in some of the practical classes was his Research Fellow, Rupert E. Billingham, who had served in the Royal Navy, completed his PhD at Oxford under "The Prof's" supervision and moved with Medawar to Birmingham when the call came. Both had been well disposed towards me in different ways. The Prof had shown great indulgence in encouraging me in my great sporting passion, field hockey, and in carrying the burden of presidential office in the Students' Union in my final year (I was the last Union President required to carry on with his studies - an onerous burden for someone anxious to secure a good degree); and Rupert (or Bill, as he was generally known) by showing his sympathy with an ex-service undergraduate and for having the brilliant idea, towards the end of my final year, of suggesting to The Prof that I might make a good junior member of his research team. I was attracted to immunology and embryology by a series of elegant and inspiring lectures by Medawar, as well as by Bill who, as a Zoology Demonstrator, had to deal quite frequently with less-than-mouthwatering experimental material and, being of a cheerful and iconoclastic disposition, liked to joke and gossip occasionally. He was at the time involved in a cattle twin study that sounded very interesting to me.

I had intended to become a school teacher and had already applied to Cambridge University for a postgraduate Diploma course in Education when The Prof asked me to become his postgraduate student. He didn't think that it would be difficult to secure a studentship from the Agricultural Research Council - those were the days - and I agreed. Little did I know that this would be the beginning of an academic life that would occupy me for the next four decades.

The Prof had meanwhile been invited to take the Jodrell Chair of Zoology at University College, London (UCL), as successor to the paleontologist, D.M.S. Watson, and Bill and I were to move with him. I graduated in the summer of 1947 and whilst The Prof took up his new Chair in the autumn, Bill and I stayed behind awaiting the installation at UCL of a small animal house and the conversion of old-fashioned laboratories. As an introduction to research Bill suggested that I might do worse than take an interest in an abstract describing the prolongation of tumor allograft survival by the in vivo use of the colloidal dye Trypan blue, and thus began my first experiments. Much to our surprise, rabbit skin allografts showed very considerably prolonged survival that did not appear to be related to stress. On moving to London a few months later I became deeply involved in the tolerance studies, which were to form the subject of my PhD thesis, and the rabbit skin allograft work was discontinued and not even written up for publication. This was unfortunate, for had I continued I might well have anticipated the role of macrophages in the induction of the immune response by several decades. However, I had other fish to fry and there began a decade of exciting and exhilarating research.

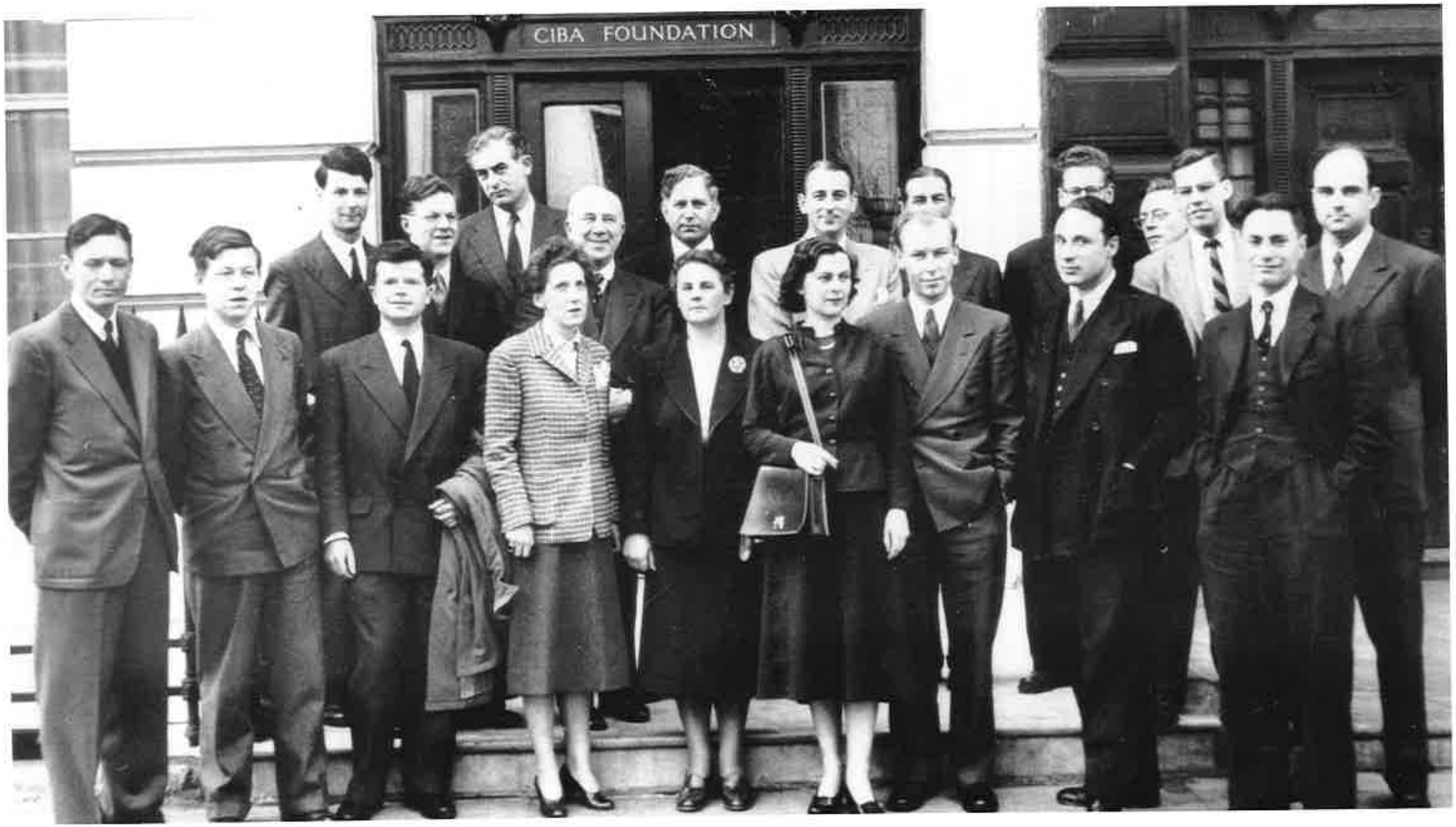
Immunological Tolerance

A number of projects were carried out, many in collaboration with Peter Medawar and Rupert Billingham - on the duration of allograft immunity, the adoptive transfer of immunity with viable cells, attempts to show that the phenomenon of immunological enhancement was applicable to skin allografts, the effects of whole body irradiation on skin graft survival, the extraction of histocompatibility antigens from living cells and their biochemical and functional properties, and the allograft response as a DTH phenomenon, to mention but a few - but I shall focus here on the discovery of tolerance and graft-versus-host disease (GvHD).

Before their move to London, Peter and Bill had completed a project on skin allograft survival in cattle dizygotic twins. Although they had known about Ray Owen's important discovery in 1945 that such twins are red cell chimeras in that, in addition to their own, they possess in varying degrees red cells patently derived from their twin, they had embarked on their cattle project because they had been asked by the Agricultural Research Council to devise a method of distinguishing clearly, and at an early age, between monozygotic and dizygotic twins. This was of agricultural interest because the female partner of dizygotic twins is nearly always sterile (a "free-martin") and is therefore not worth rearing. It was only when their expectation was turned upside down in that dizygotic twins accepted each other's skin just as happily as monozygotic twins, that they realized that red cell chimerism and skin graft acceptance owed their existence to the same event, ie, the exchange of hemopoietic progenitor cell once the placental parabiosis that is so characteristic of cattle twins becomes established. It was Lillie who had demonstrated the fused placentae of such twins at the turn of the century and Owen who had used this fact as an explanation for red cell chimerism. Spurred on by Owen's seminal discovery and their own results, as well as by the brilliant speculations of Burnet and Fenner in their monograph *The Production of Antibodies*, Peter Medawar decided to embark on the experimental verification of the phenomenon of immunological tolerance. Bill and I were to be his close collaborators and inbred mice the experimental subjects. By then we had standardized skin allograft survival in several strain combinations, notably A/Jax to CBA and the other way round, and established median survival times with standard deviations so that even a relatively trivial prolongation of graft survival could be recognized.

Although Bill and I did much of the later work, Peter was very much involved in the early attempts to inoculate viable allogeneic spleen cells into fetuses of the recipient strain. Peter had his own small laboratory where he liked to work on his own and where much of the work on extraction and characterization of histocompatibility antigens was done, in collaboration with M. Ruszkiewicz, but much of the tolerance work was carried out in Bill's much larger lab, where Bill and I worked together (my own lab was on another floor and was used mainly for histological purposes). Later, when Peter's other commitments became very heavy, he dropped in whenever he had some spare time in order to keep abreast of progress being made, to discuss data, and to plan further experiments. Many of these chats took place whilst Bill and I were engaged in fairly routine skin grafting of our experimental animals, and one vivid memory I have is of Peter, during these talks, taking a small pair of curved scissors from a hook and cutting his nails. Bill and I thought this was rather hilarious; I still possess the scissors and use them for the same purpose, though in privacy.

Our first approach, in the spring of 1952, was to anesthetize pregnant mice and to inject the fetuses via a radical laparotomy. We soon found that this could not be done successfully in fetuses younger than 16-17 days, and even then we encountered a high proportion of spontaneous abortions or sickly neonates. Our next step was to merely open up the mother's abdominal skin and to inject the cells through the semitransparent body wall. This reduced the proportion of aborted litters but made it far more difficult to direct the needle point into what we hoped to be the fetal body cavity, and injections were far more



Ciba Foundation Symposium on Preservation and Transplantation of Normal Tissues, 1954;
Back row: L. Brent (1st from left), P.B. Medawar (3rd from left), W.R. Earle (4th from left), E. Eichwald (3rd from right);
Front row: W.P. Longmire (1st from left), P.A. Gorer (2nd from right), W. Dempster (1st from right).

hit-and-miss. Nevertheless, after about nine months of hard and rather frustrating work we found that some donor strain skin grafts transplanted to survivors six to eight weeks after birth showed a highly significant prolongation of survival, and one or two survived permanently. This renewed our enthusiasm, and it now became a matter of accumulating enough unresponsive mice to study the properties of this "tolerance," such as its specificity, duration, and vulnerability to the adoptive transfer of viable spleen or lymph node cells that were syngeneic with the tolerant recipient, either naive or presensitized. The fact that we were able to break tolerance within three weeks by the introduction of naive spleen cells convinced us that we were dealing with a "central" form of suppression (later identified as clonal deletion) rather than with an active suppressive mechanism. Although suppressor T cells were unknown at that time, we ruled out enhancing antibodies or complexes as the mediator of tolerance, thus distinguishing clearly between enhancement and tolerance.

I recall one or two amusing incidents. One involved the escape of a female mouse bearing a gloriously healthy allograft. Being of rather ancient vintage, Bill's lab offered a great many escape routes, and the mouse, after hot pursuit, disappeared into a crack between wall and floor. We were desolate but, after trying all kinds of enticements, managed to capture our prey with the aid of a male placed in a small wire cage on the floor. On another occasion we came across an injected litter in which all its members appeared to be fully and permanently tolerant - our first *major* success. The result was so good that we became suspicious: might we have been supplied, accidentally, with F1 hybrids that would genetically accept the donor strain grafts? Suitable investigations did indeed show this to have happened. What a letdown! On a different note: Bill and I were working in his lab when Peter opened the door in a state of high excitement: the young Queen was about to travel past the College along Gower Street, and how about making a dash for it and giving her a cheer? Although not quite such ardent royalists, we duly obliged. It is amusing to speculate whether even in those early days Peter had a premonition of royal favors to come: he was eventually knighted, awarded the Order of Merit, and made a Companion of Honour.

The first time that we presented the world with our findings on tolerance was at a meeting of the British Society of Experimental Biology. It was characteristic of Peter's generosity (and Bill's too, for he had agreed to it) that he should have asked me, the junior member of what was rapidly becoming known in the United States as "the Holy Trinity," to present our findings. The hall was packed and the concept of tolerance, with its implications not only for transplantation but also for autoimmunity, aroused a great deal of interest. Our *Nature* paper appeared in the same year (1953) and although we published a number of other papers, our overall findings in the mouse, rabbit, and the chicken were not fully published until 1956, when a massive paper with color prints (a fairly novel and at that time certainly very expensive device) appeared in *Philosophical Transactions*, in which all the implications of acquired immunological tolerance, as we had called it, were fully discussed. Two years earlier I had presented my PhD thesis - a rather slim volume compared with some of the bulky tomes that land on my desk with a thump these days. This might be an appropriate occasion on which to acknowledge that Bill was our photographer and his slides and photographs were always of the highest standard; neither Peter nor I had a camera and we were always much indebted to Bill for his expertise. A number of these slides illustrating our early critical experiments still form a highly valued part of my slide collection.

Life at that time was indeed heady. All three of us, well supported by our one and only technician, Trevor Courtney, worked a very full day, and I had the additional incentive and responsibility of preparing my PhD thesis. Tolerance apart, the Medawar team - and that is what we were in the best sense of the word, although Peter was the undisputed leader - made numerous other contributions to the literature, and when I published a review on transplantation immunity in 1958 I was able to refer to the vast majority of interesting papers that had thus far been published in the space of 23 printed pages! Being a loyal family man with young children, Bill was usually the first to leave the department; Peter was as often as not still typing furiously in his small office by the time I decided to call it a day, for he was punctilious in typing up notes of the day's work and was also much in demand as a lecturer nationally and internationally. My first visit to the United States was, I think, in 1954 when I attended one of the Gordon conferences to talk about tolerance; I remember with pleasure meeting Merrill Chase there and the interest he took in our work and his kindness towards me. This was a time when interesting observations in the lab came thick and fast, and I became so absorbed in the work that my young wife (we married in 1955) saw rather less of me than was good for our marriage. Peter had become something of a role model for me, but not surprisingly I felt stretched to emulate him both in his physical energy and his intellectual vigor.

Meanwhile Milan Hašek, working in Prague, had published a short paper in *Folia Biologica* on a method of bringing about the parabiosis of chick embryos, with successful hatching at the end of the incubation period in a number of cases. (For further memories of Milan, see below.) This interested us quite a lot, for although Hašek had shown that such parabionts did not produce normal titers of agglutinating antibodies to each other's red cells - a finding he interpreted as "vegetative hybridization" - we were anxious to discover whether this hyporesponsiveness extended to skin grafts. His paper was brought to our notice by a Russian-speaking colleague, Alex Comfort, and we began a series of experiments establishing parabiotic union between 10-day old Rhode Island Red and White Leghorn embryos. The work was frustrating because of a high mortality rate of one or the other parabiont, but we were eventually rewarded with success. Not only were the parabionts red cell chimeras (we were able to ascertain that with the aid of some antichicken red cell sera kindly provided by Ray Owen, by then firmly established at Caltech), but they were firmly tolerant of each other's skin grafts transplanted two weeks after hatching. That raised the possibility that the vasculature of chick embryos in double yolked eggs might fuse spontaneously and mimic the situation in cattle twins. So it did: not only did Trypan blue injected into a chorioallantoic vein of one embryo appear instantly in the circulation of the other, but the twins proved to be red cell chimeras and tolerant to each other's skin grafts. We had therefore uncovered a perfect replica of the cattle story, and subsequently it was shown by others that red cell chimerism occurs as a rare event in human dizygotic twins, too.

This study involved us in an amusing incident. One of the British "tabloid" newspapers had become interested in the chick work and had appealed to chicken farmers to make themselves known if they were in possession of two chicks that had hatched out of the same egg. Lo and behold, a farmer phoned one day and Peter arranged to see him to receive such a pair of young chicks. The farmer said he would bring his wife, too. It was Peter who dealt with this, with Bill and myself waiting in the wings in a state of some hilarity for we had noticed that the farmer's wife was a considerable beauty: would her presence perhaps undermine Peter's judgment? It did! The

Donald Mickey (far left), Anne Mclaren (2nd from left), L. Brent (2nd from right), and R.E. Billingham (far right) at the Ciba Symposium in 1954.

L. Brent and P.B. Medawar en route to Harwell in 1956.

couple duly departed, 20 pounds having changed hands (a lot of money in those days, my annual studentship was worth about 450 pounds), but the chicks were ours. The application of Ray Owen's red cell typing reagents and an exchange of skin grafts soon showed that Peter had been duped! I don't think that he ever saw the funny side of this transaction.

After several years of laborious mouse work, with a high rate of abortions and postnatal mortality, Bill and I decided to explore whether the neonatal mouse could be made tolerant. We assumed that at that late stage only an intravenous infusion of allogeneic cells would stand any chance of success, and after numerous attempts using a 30 gauge needle we settled for the anterior facial vein or one of the two branches of the sigmoid sinus. The latter caused less bleeding, and it therefore became the preferred route. Having shown that a relatively low dose of allogeneic cells induced full tolerance to donor strain skin, this methodological innovation, which was quickly taken up by other laboratories, notably Robert Good's team in Minneapolis (I visited their laboratory on my way to Caltech in 1956, before our *Transplantation Bulletin* paper had been published and demonstrated the technique to C. Martinez and his colleagues), opened up the study of tolerance and enabled us and others to study the parameters of tolerance in a more quantitative manner. Progress was now far more rapid. Bill and I injected a great many neonates, but now using F1 hybrid spleen cells in order to avoid GvHD. The technique was quite taxing and required a very steady hand on the part of the mouse holder (usually Bill) and the inoculator. After one lengthy session hunched over the operating table I was unable to straighten my back again and had to make my way home by bus ignominiously doubled up, despite the ministrations of a pharmaceutical chemist on the way. My wife and I were expected at a dinner party that night, but my contribution to the evening's proceedings was minimal, apart from affording our hosts some good-natured and concerned amusement. Lee Rayfield, a PhD student of mine in the eighties, taught himself to both hold and inject neonatal mice - a considerable feat that saved manpower and avoided the danger of triggering the kind of seizure that I had experienced.

I must recall one incident that reflects considerable credit on both Peter and Bill. In 1954 my fiancee Joanne Manley and I had accepted from her brother a ride in his car to the north of England in order to spend Christmas with her parents. It was Christmas Eve and as we passed through Lichfield we decided to spend a few minutes inside the magnificent cathedral. We left the sports car, with suitcases piled on the back seat, in the busy market place and were utterly dismayed, on our return, to find that thanks to a defective lock my case had been stolen. This would not have been particularly remarkable had it not been for the fact that it contained some laboratory notebooks with records of our tolerance experiments. I was absolutely frantic but nonetheless failed to impress on the local police, whose thoughts were no doubt on Christmas dinner, the importance of this loss. I phoned Peter as soon as we had reached our destination. He remained admirably calm, managed to commiserate with me and reminded me that most of the data had either already been published or lay embedded in the first draft of my PhD thesis. Bill was subsequently equally supportive, and the damage did, in fact, prove to be minimal.

The Discovery of Runt Disease (GvHD)

The use of the intravenous route in murine neonates led directly to the discovery of GvHD. For some time Bill and I continued to use fully allogeneic spleen cells as the tolerogen and we were puzzled that, whilst the neonates survived the inoculations quite happily, many of them died within three weeks, even though the mothers seemed to be looking after their litters quite normally in the first week. Careful autopsies of some of the young mice revealed gross abnormalities of their lymphoid tissues - enlarged spleens and atrophied lymph nodes and thymuses were among the most obvious. The growth of these mice was severely retarded - hence the term runt disease - and one clinical symptom was severe diarrhea. I remember the day on which the penny dropped, when we rushed into Peter's office to show him some autopsies and tentatively suggested that the condition might have been caused by an immunological reaction of the injected allogeneic cells against host histocompatibility antigens. Peter agreed and became equally excited. He felt, however, that this was a discovery that the two of us had made and that we should continue to analyze the phenomenon, and characteristically he refused to have his name on any of the papers published by us, although we felt it perfectly appropriate for him to be a co-author. I have tried to emulate him in this throughout my subsequent career, but the idea that senior workers should be co-authors only if they have made a direct contribution to the work seems to be unfashionable these days.

The early results on runt disease were published in the same 1957 paper in *Transplantation Bulletin* in which we had described the intravenous route of neonatal inoculation. The studies that proved conclusively that runt disease was caused by a graft-versus-host reaction were not published until 1959, a year later than need have been the case because I took a sabbatical in the summer of 1956 to spend a year as a Rockefeller Research Fellow in Ray Owen's lab at Caltech, and by the time I returned Bill had left to join the Wistar Institute. The first draft of the massive manuscript, which was to be published as another *Philosophical Transactions* contribution, was therefore considerably delayed. I must take much of the responsibility for this, for although Bill had produced a first draft in 1957 it took me an inordinately long time to revise and rewrite it, having on my return to London become embroiled with other projects, notably the work with Jean Brown, a PhD student, on the expression of the allograft response as a cutaneous DTH reaction in guinea pigs. Meanwhile, Morten Simonsen had come across GvHD in chick embryos following the intravenous injection of allogeneic lymphoid cells, splenomegaly being one of the most dramatic consequences. His was an entirely independent discovery, also published in 1957, and he went on to describe the quantitative splenomegaly assay that became such a useful tool in the analysis of GvHD. Morten became a regular visitor to our lab and we thus had the opportunity of exchanging information on progress in London and in Copenhagen.

In 1957 John Loutit, David Barnes, and their colleagues at Harwell were studying the effects of bone marrow transplantation in lethally irradiated mice - as were several groups in the United States, notably at Oakridge. The "secondary disease" described by them seemed to us to bear a close resemblance to runt disease, and, after my return to London, Peter Medawar and I travelled by car to Harwell to discuss with John Loutit's group the probability that both syndromes owed their existence to GvHD. They were intrigued to hear of the investigations Bill and I had carried out and took up the idea with great enthusiasm.

Peter and Bill

Peter had a great deal of charisma. He was tall and strongly built (a feature of which he made good use when playing cricket and squash) and extremely handsome. He made an impression on people as soon as he entered a room and, what with his intellectual stature, cultural interests and attainments (mathematics, music, literature, and philosophy all came within his remit), and social graces, he was immensely popular at all levels. He didn't suffer fools gladly - a characteristic that became less marked later in life after his brain hemorrhage - and could be quite cutting about people who did not measure up to his expectations. He was a delight to work with, and although I eventually felt that I had to get away from him, the 14 years I worked with him at University College and later at the National Institute for Medical Research, where he became Director, were undoubtedly the most stimulating and enjoyable of my scientific life; Peter has gone on record with the same sentiments. He and I got along extremely well, partly because we had similar interests such as music and played chess, squash, and cricket together. Before I got married he frequently invited me for a meal at his home in Hampstead where Jean, who never seemed to be ruffled by the arrival of another mouth to feed, ruled the roost most graciously. Despite a lot of friendly bonhomie there was, nevertheless, some distance between us, and in retrospect it interests me that he never talked to me about my early background and the fate of my family, probably because of a certain personal reticence on his part and because he felt it might have been too painful a subject. Except when listening to music he tended to keep his emotions on a pretty tight rein.

Peter's standing as a scientist and the appraisal of his many contributions and qualities that made him one of the dominant scientists of his generation have been discussed in obituaries, appreciations, and biographies. I shall restrict myself here to a few disjointed observations based on my years with him. Despite his great intellectual powers he was at his best - some of his writings excepted - as an experimental scientist, and he always said that he liked nothing better than to work with his own hands in the lab. He was so punctilious that he insisted on washing his own glassware, even after he had become Director of NIMR. Skin grafting sessions provided him with relaxation and allowed the three of us to discuss the progress of our work and to pool our ideas about future experiments. He was a remarkably deft operator, especially in view of the size of his hands. The equipment at our disposal was quite limited and his joy was unconfined when he received his first high-speed centrifuge, courtesy of NIH. But Peter's approach throughout his life had been to think up significant experiments that could be tackled relatively easily with the simplest of tools, and skin allografts as an analytical device in rodents continued to be his chosen vehicle. He did not believe in large research teams and his never exceeded one or two postdocs at a time, with the same number of postgraduate students.

One day in the autumn of 1960 (October 20), Peter burst into my lab in a state of great elation, asking me how I would like to win the Nobel Prize. I replied that I would indeed rather like that. He had just received a phone call from a journalist in Stockholm, with the first intimation that he had been awarded the Nobel Prize in Medicine jointly with MacFarlane Burnet. With typical generosity he shared the financial award with his research colleagues, and I was able to buy my first car. Having achieved fame his telephone never ceased to ring, even after the daily departure of his secretary. One evening I overheard him answer the phone. His voice had assumed an extreme falsetto: "You wish to speak to Professor Medawar? Ah, what a pity, unfortunately he is not available..." I almost doubled up with laughter.

Roy Calne likes to tell the story of how Peter, after a scintillating lecture in Cambridge, was asked whether the tolerance work would ever find clinical application. Peter's reply was apparently brief and to the point: "Absolutely none." That was before specific unresponsiveness had been induced in adult animals and it was therefore a perfectly reasonable point of view, bearing in mind the immunological maturity of the human neonate.

Bill's qualities were wonderfully complementary to Peter's. He was (and still is) an engaging man, with a very practical and down to earth approach to life as well as to science. He lacked Peter's social graces and interests (though they enjoyed discussing autobiographies such as that by Winston Churchill, one of Bill's passions) and my impression was that they never grew very close. However, there was an immense amount of mutual respect between them and Peter was greatly dependent on Bill. I liked working with Bill and I enjoyed his mischievous sense of humor. He may not have been Peter's intellectual equal but he was a most ingenious and innovative experimentalist who never let go of a problem once he had become interested in it, and as often as not an experimental solution was found. Among Bill's excellent qualities were his optimism and tenacity in the face of difficulties that might well have persuaded Peter to throw in the towel.

When Jean Hamburger, who has made such important contributions to the development of renal transplantation, introduced me at the end of the 1976 Transplantation Congress in New York before I gave my Presidential Address, he expressed his disappointment and sense of outrage that Bill and I had not been selected to share the Nobel Prize with Peter and MacFarlane Burnet. I had never discussed this question with Bill, who was sitting in the audience as the outgoing President of The Transplantation Society. I replied that so far as I was concerned I had no complaints and that I thought that the same applied to Bill, too. Subsequently I talked to Bill about this, and I was mightily relieved to find that he concurred. I have nonetheless always believed that Bill should indeed have shared the honor, for not only was he a key man throughout the early tolerance work but he had been involved in the cattle work that had preceded it. It is not the only mistake made by the Nobel Prize Committee over the years.

With my year at Caltech in 1956-57 to work in Ray Owen's laboratory the wheel came full circle, for it was Ray's 1945 paper on cattle twins that had provided the first crucial building block in the tolerance story. Ray was at that time already deeply involved with teaching, admissions, and the refereeing of grant applications, but he was extremely well informed and he kept a sharp eye on the literature in genetics, immunogenetics, and molecular biology. He struck me as a highly intelligent, knowledgable, and perspicacious scientist who generally preferred to do research through his postgraduate students. He got up (and still does!) at the crack of dawn and liked to be brewing coffee in his office by 8 AM - rather a culture shock to this effete European. One of his junior colleagues was Jim Berrian, who was on secondment from the Navy to do his PhD, and we decided to carry out a joint project to show that there are "cell-bound antibodies" (we would now call them receptors) on splenic and lymph node cells. Our study, which depended on our recently established procedure for the extraction of noncellular and biologically active histocompatibility antigens, was carried out before T and B lymphocytes had been identified. It established the point, but we made the mistake of publishing it exclusively in the *Proceedings of the New York Academy of Sciences*, where it remained buried. On my return to London I became embroiled with other projects and did not follow up these experiments - a pity, for what we had described as cell-bound antibodies could well have led to a much earlier appreciation of the existence and role of lymphocyte receptors.

Ray and his wife June were charming and attentive hosts during our stay in Pasadena, and we were much indebted to them for all manner of kindnesses, not least among them the arranging of a special fee for the birth of our first child Simon, moral and technical support in the purchase of our first car - a remarkably ancient but functional Buick - and care of our child for a week whilst we hiked in the upper Sierras with some old friends and a delinquent Mexican burro. It has been one of the pleasures of my life to have been able to count Ray and June among my friends.

Milan Hašek

I have indicated above that Milan Hašek published his work on the parabiosis of chick embryos in 1953 and that he chose to interpret the hyporesponsiveness as "vegetative hybridization". This was in accord with the then current ideology, in the Soviet Union and other East European countries, as promulgated by the politically inspired theories of Michurin and Lysenko: the mistaken belief in the power of the environment to alter the genetic material of adult organisms. Peter Medawar and I met Milan at an embryological congress in Brussels in 1954 and told him of our tolerance studies. Milan was far too intelligent not to realize that he had fallen into an ideological trap in the interpretation of his experiments, and in 1955, together with T. Hraba, he published a follow-up paper in *Nature* in which the political polemics had been dropped and the data were reinterpreted in the light of western studies. He and his colleagues subsequently made a number of pertinent and valuable contributions to the tolerance literature and, in doing so, made the Prague Institute of Genetics and Experimental Biology by far the most advanced and influential in Eastern Europe.

Although Hašek and Medawar were vastly different in many respects, they shared the same physique and restless energy. Milan and his colleagues became good friends with us over the years and I have many pleasant memories of their hospitality at a time when conditions in Czechoslovakia were economically stringent and politically fraught. Milan had an unlimited (or so it seemed) capacity for vodka, and it was most entertaining to watch him arm-wrestling with Peter after an evening meal, or demonstrating his prowess at balancing heavy chairs one-handedly high above his head. It is tragic that this "good communist" was later, having signed the Dubcek Declaration, deprived of his Directorship and the right to function as a scientist, and that after a partial rehabilitation, he was eventually impelled to commit suicide.

Visitors to the Department of Zoology

I would not wish to end these recollections without mentioning some of the visitors Peter and the tolerance work attracted to the department, as well as our contacts with Peter Gorer at Guy's Hospital who was at that time working on the genetics and serology of H-2. I think that the two Peters, though admiring each other's work a great deal, were somewhat wary of each other in the mid-fifties. The reason, I suspect, was not only that they were temperamentally very different, but that they were at opposite ends of the controversy concerning the role of antibodies and cells in the destruction of allografts, exacerbated by the fact that Gorer at first refused to approve the PhD thesis of Av Mitchison, who had been supervised by Medawar. (It was scientifically a very good thesis, as one might expect, but its presentation had apparently not been to Gorer's satisfaction.) Nonetheless, the two Peters met for dinner in a restaurant from time to time, accompanied by one or two of their postdocs, to discuss recent developments in their respective areas and mutual problems. These occasions were always great fun and gave me the opportunity of not only getting to know Gorer (he was a genial nonstop smoker whose arguments were not always easy to follow, if only because a cigarette usually dangled from his mouth when holding forth) but also Bernard Amos, Teddy Boyce, and later Richard Batchelor, all of whom worked with Gorer.

MacFarlane Burnet dropped by whenever one of his world tours took him through London, and we invariably took him at the end of the day to the local public house (bar) where we enjoyed our discussions over a glass of beer, sometimes interrupted by a game of bar billiards. Burnet usually had some interesting new idea up his sleeve, developed on his travels: he had a genius for picking up experimental data that suited his ideas and ignoring those that opposed them, and his clonal selection hypothesis was his crowning glory. It made us realize that what we had interpreted as a form of "central failure" of responsiveness in tolerance was almost certainly clonal deletion or inactivation, and so it turned out to be. The three of us used to think of Burnet as "a dry old stick," certainly not given to small talk, with a less than glowing personality.

Among other visitors there stand out Göran and Erna Möller (who chose to spend part of their honeymoon in the department!) and Jean Dausset, who told us about his very early serological work using a leukoagglutination method. I don't know whether Jean felt that he had received a very sympathetic hearing, for the three of us were at that time somewhat besotted by the concept that antibodies were a great irrelevance in allograft rejection, and we may well have felt that he was wasting his time!

Finally, several postdoctoral Fellows spent a year or more in the department, either working with Peter or pursuing their own interests. Peter chose not to involve any of them in the tolerance studies. The first was Paul Russell (1954-55), who worked on the effects of adrenalectomy on the allograft response and whose first child was born in London. He was followed by Bill Hildemann, who exchanged with me whilst I was spending my year with Ray Owen at Caltech, and after my return we welcomed Paul Terasaki, who developed his interest in cytotoxic antibodies during his stay with us. It is pleasant to record that the two Pauls became lifelong friends of mine.

I look back to life in the fifties with a sense of great excitement. Those years involved me in the discovery of two major immunological phenomena and a lot more besides, and they form the bedrock of my scientific life and the forging of many friendships.

It is gratifying that there is now so much renewed interest in tolerance and its application to adults, and I would guess that by the beginning of the next century active tolerance induction will have become possible in human organ graft recipients, revolutionizing the treatment of human disease.

CURRICULUM VITAE

Leslie Brent

PERSONAL

Born:	July 5, 1925: Köslin, Germany
Marital Status:	Married to Joanne Manley, 1955; Divorced 1991 3 Children: Simon (34), Susanna (33), Jennifer (28)

EDUCATION

1947-51	University of Birmingham, B.Sc.
1951-54	University College, London, Ph.D.

MILITARY SERVICE

1943-47	British Infantry, demobilized with rank of Captain

POSITIONS

1942-43	Laboratory technician, Birmingham Central Technical College
1954-56	Assistant Lecturer, Department of Zoology, UCL
1956-62	Lecturer, Department of Zoology, UCL
1965-69	Scientist, National Institute for Medical Research; Professor of Zoology, University of Southampton
1969-90	Professor of Immunology, St. Mary's Hospital Medical School

PROFESSIONAL SOCIETIES

British Transplantation Society

1972-75	Founder General Secretary

2nd International Congress of Immunology

1974	Member of Organizing Committee

The Transplantation Society

1972-74	Vice-President
1976-78	President
1982	Chairman, L.C.O.C., 9th International Congress

AWARDS

1951	Vice-Chancellor's Prize for the most outstanding student of the year
1956-57	Rockefeller Foundation Research Fellowship
1962	Fellowship of Institute of Biology
1964	Scientific Medal of the Zoological Society of London
1972	Honorary Member of Scandinavian Society for Immunology
1977	Honorary Member, Southern Africa Transplantation Society
1978	Honorary Member, American Society of Transplant Surgeons
1986	Honorary Member, Royal College of Physicians
1988	Honorary Member, British Transplantation Society
1990	Emeritus Professor, University of London

EDITORIAL BOARDS AND EDITORSHIPS

1962-67	Transplantation (European Editor)
1974	Progress in Immunology (Co-editor)
1983	Proceedings of the 9th International Congress of The Transplantation Society (Co-editor)
1983-90	Immunology Letters (British Editor)
1989	Organ Transplantation: Current Clinical and Immunological Concepts (Co-editor)
1989	Sir Peter Medawar Symposium (Editor)
	Member of Advisory Board of a number of journals

COUNCIL AND ADVISORY COMMITTEES

1950-51	President, Guild of Undergraduates, University of Birmingham
1988-90	Founder Chairman, London University Joint Advisory Committee in Immunology
1986-90	Scientific Advisor, Blond McIndoe Medical Research Centre

PUBLICATIONS

Total: About 200 papers in a variety of journals, chapters in books

RESEARCH INTERESTS

The biological basis of tranplantation immunity; role of antibodies and cells in allograft rejection; tolerance and enhancement; specific unresponsiveness to histocompatibility antigens in adult animals; antilymphocyte serum and other nonspecific immunosuppressive agents; the mechanism and prevention of GvHD; NK cells; antigen presentation; the immunological maturity of the human fetus; bone marrow transplantation to neonatal and adult mice, and to the cynomolgus fetus; the immunological basis of psoriasis; the history of transplantation immunology.

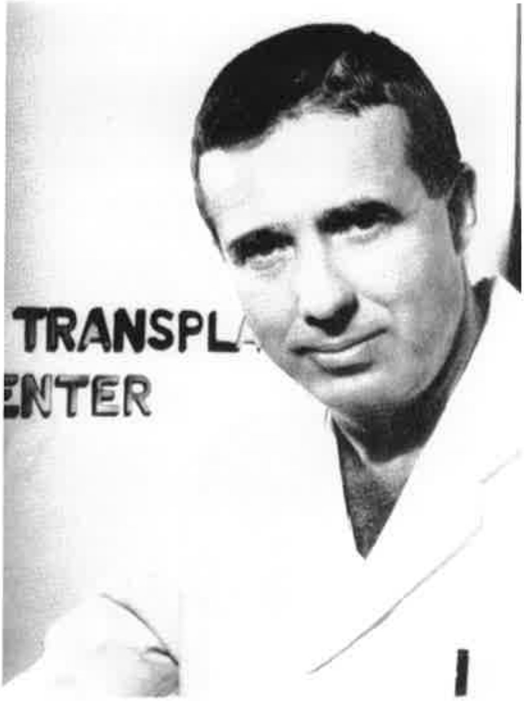
OTHER INTERESTS

Music, choral singing, fell walking and mountain climbing, skiing, novels, chess, and cricket; formerly hockey for British Universities.

David M. Hume

1917 - 1973

As remembered by H.M. Lee



David M. Hume

Recollections of David M. Hume

Written by Dr. H.M. Lee for *Chimera*

Dr. Hume came to the Medical College of Virginia in Richmond Virginia in 1956 at the age of 39 to succeed Dr. I. A. Bigger as Chairman of the Department of Surgery. He was recruited from Peter Bent Brigham Hospital in Boston where he was continuing his surgical endocrinology and organ transplantation research after returning from a second Naval stint. Dr. Hartwell Harrison, Urologist, who was a team member of the earlier kidney transplant experiments, was a Virginian and I believe that had something to do with his being recruited to Virginia to modernize the provincial surgery department and model it after the Boston style with strong teaching and research as well as clinical performance.

I was a junior resident in the surgical department at the time. I was not privy to the many political skirmishes which developed in the early tenure of Dr. Hume as the leader of the surgical department. Many political battles were fought with the local establishment. I remember on one occasion a newly elected President of the Medical Society of the city publicly criticized the surgical department for leaning too much toward research and forgetting to treat the ills of Virginia. Eventually, Dr. Hume was recognized as an undisputed leader of the medical scene in Virginia and he made the department into a vigorous, internationally recognized one. There were whisperings at the beginning that Dr. Hume was not terribly good in surgical technique. By the time I began to know him more closely, he developed into a master surgeon, even in the operating arena with his characteristic methodical self training. As he proceeded in surgery, he would dictate the technical steps of the involved surgery, step-by-step to his private circulating nurse, and then the second time around he would be modifying the first step-by-step method, and by the third or fourth time, he had a very streamlined, clear-cut cookbook style method for performing this surgery. As the first assistant in the operating room, I would often wonder how he would get out from a tight spot or handle the unexpected complication in the situation where I thought there was no way out. Inevitably, he'd come up with a new, innovative, unorthodox approach to the problem.

He was a man of inexhaustible energy and optimism, and he could not wait; he was racing against his own clock (10 days work into one). An associate walked into his office one morning and found him sitting there having worked all night on an emergency case in the operating room. He looked exhausted, almost ashen gray, but when asked how he was feeling, he explained that he was "feeling great." His associate said, "I believe Dave really believed what he said, he indeed was feeling great." That was the kind of man he was.

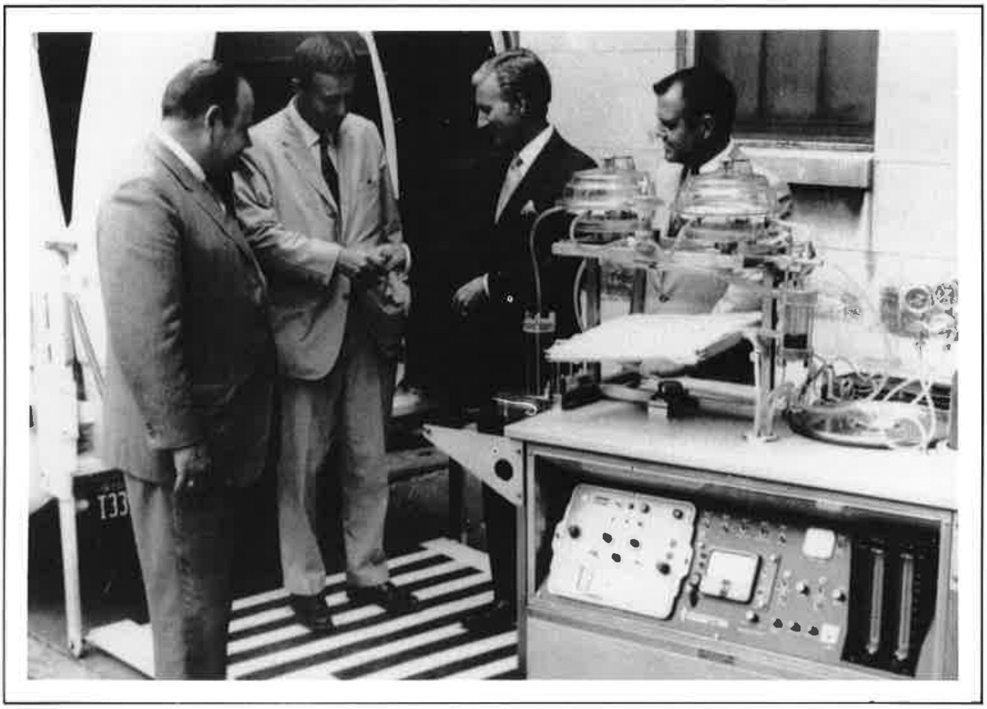
Midnight ward rounds were almost Dr. Hume's trademark. It was not uncommon to see the house officers making midnight rounds. This (no clock) concept of activity extended into the research lab and at times, some of the clinical research, such as the baboon cross-circulation, xenograft, and so on would be done in the evening or the middle of the night with some of the fellows in the research lab who were running around in the dark of night.

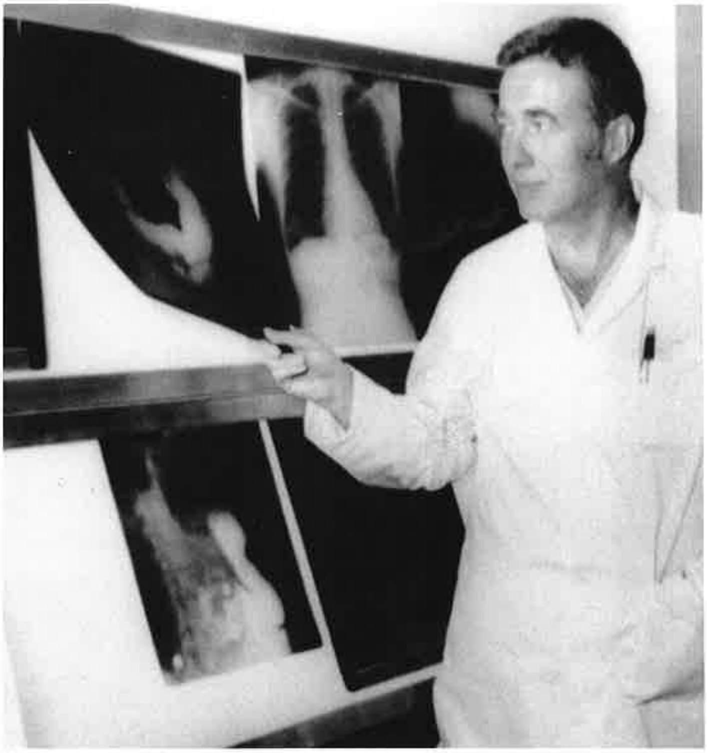
His intellectual curiosity was unlimited. His mentor, Dr. Francis Moore, termed him as "restless genius" and others compared him to the "unreasonable man" of George Bernard Shaw's description. He would not accept any old established rule or custom unchallenged. He was arrogant against blind authority. His innovation extended from minor trivia to major concepts. In a light-hearted vein, one day during rounds a resident mentioned that he was having difficulty feeding a patient three meals a day because the patient refused and insisted on having a meal only once or twice a day. Dr. Hume immediately asked, "What's wrong with that? Why not one meal??"

His compulsion to seek excellence influenced and inspired many of his students and colleagues. He would not take no for an answer, and he tried to find newer and better methods in research and clinical care. Not finding any precedence did not deter him; he would be insistent that we find a solution to what was considered to be an insurmountable problem. In the infancy of parenteral hyperalimentation, we had a young child who had to have almost the entire length of the small intestine removed, creating an almost impossible "short gut" syndrome to sustain life. With his innovative attitude as well as his tenacity, he devised a portable long-term basis alimentation scheme for the child to return to her home environment in New Jersey. I believe that this was the first case of long-term hyperalimentation that was ever achieved.

He was an excellent teacher; a man who set an example and taught by doing. He delighted in provoking, debating, and arguing with his students and experts alike, always addressing his adversaries as equals be it a student, intern, or a world renowned expert. He created a free and stimulating atmosphere for students, fellows, and associates. It was not unusual to find him in the late evening or the middle of the night discussing or arguing with medical students or interns during midnight rounds. His discourse was precise, concise, and lucid, be it written or spoken. We often wondered why, after arguing with him, the problem looked so simple.

His unbound, youthful enthusiasm was infectious and readily transmitted to people around him. We would walk into his office with a little idea, small project, or a very simple clinical case and then walk out with a sense of elation, adventure, and energized with new fervor. As to his charm and wit we often said, "Watch out, he'll charm your pants off." He maintained a unique zest and sense of adventure to his last day. "He





never grew up." He was a Renaissance man with a depth of intellect and wide ranging interests from surgery, medicine, and the world as a whole. Watching him was like watching a great athlete perform in the intellectual arena; we'd marvel at his sheer ability to think through a complex problem. It was like watching a great musician perform. You were mesmerized with his precision and breadth of interpretation. Surgical Grand Rounds was one of those forums. He would be arguing with guest professors, experts in diverse subjects, holding his own with his sharp questions and incisive criticism. It was not only a learning experience but also beautiful and fun to watch.

He was compassionate and had a warm understanding with a knack for putting people at ease. In the hospital ward we would often find him sitting with old, uneducated patients holding their hands, explaining and comforting them, and at times carrying their bed pans. His boyish grin radiated his warmth and caring. He imparted a sense of friendship and loyalty to the people around him. I not only felt him as being a mentor and teacher, but also a personal friend.

Under this formidable picture of the world leader of surgery, he retained a boyish mischievousness to the last. This was manifested not only in the family or departmental picnic, playing around with little children on motor bike rides or horseback riding, swimming, racing, 100 yard dash and so on. It was manifested in the New Year's Eve parties, dancing away on the floor, wrestling at the end of a dinner party in the formal setting, in the loud singing fests with his friends at the piano bar.

To him, there was nothing impossible. He felt he could do anything if it was thought out well and pursued with his bulldog tenacity. He was self confident that he could conquer the insurmountable. It was his free spirit, self confidence, and self reliance, which in the end, killed him. As one of his former residents spoke, it was befitting that he was struck by a mountain while flying in the air as a pilot of his ship.

BIOGRAPHICAL SKETCH

David Milford Hume, M.D.
Medical College of Virginia
Richmond, Virginia

Dr. Hume was born in Muskegan, Michigan in 1917 and received his M.D. degree from the University of Chicago in 1943. During the time at Chicago he worked under Dr. William Bloom in the Department of Anatomy on hypothalamic-pituitary-renal interrelationships. Subsequent to this he did his surgical training in Boston at the Peter Bent Brigham Hospital, punctuated by time spent in the Navy and two years in the laboratory as a Harvey Cushing Fellow.

In the laboratory he carried out investigation on the hypothalamic control of pituitary-adrenocortical secretion in dogs using sterotactic ablation and remote control stimulation and began experimental work on renal homotransplantation.

In 1951, after completing the chief residency at Peter Bent Brigham, he became Director of the Laboratory for Surgical Research at Harvard. In that year and the next, in conjunction with Dr. John Merrill, of the Renal Physiology Division of the Department of Medicine, he carried out nine cadaver donor renal homotransplants in patients with terminal renal failure. Four of these patients were the first organ transplants in man to show sufficient function to maintain the life of the host, and one untreated transplant functioned for six months. Attempts were made at immunosuppression with corticosteroids, but the supply was too limited to continue the treatment for more than a few days.

From 1953 to 1955 he was again on duty in the Navy stationed at the Naval Medical Research Institute in Bethesda. Here the work continued on hypothalamic-pituitary-adrenal relationships and renal transplantation.

After returning to the Peter Bent Brigham Hospital for a year he went to Richmond, Virginia in 1956 as Stuart McGuire Professor of Surgery and Chairman of the Department. The first twin transplant there was done in 1957, and the current homotransplant program was begun in 1962.

Honors include Francis Amory award of the American Academy of Arts and Sciences in 1962 (co-recipient), outstanding Harvard alumnus of the State of Virginia in 1968, Valentine award by the New York Academy of Medicine in 1970, Humanitarian award by the Richmond Chapter of Hadassah in 1971, and the Distinguished Service Medal from the University of Chicago in 1971. In January 1972, Dr. Hume received the Distinguished Achievement Award from Modern Medicine Magazine.

CURRICULUM VITAE

David Milford Hume

October 21, 1917 - May 19, 1973

EDUCATION

1940	Harvard University, B.S.
1943	University of Chicago School of Medicine, M.D.

BOARD CERTIFICATION

American Board of Surgery

MILITARY SERVICE

1945-46	U.S. Navy Surgeon, Aiea Hts., Pearl Harbor
1953-55	Naval Medical Research Institute, Bethesda, Maryland (Lt. Commander, MC, USNR)

POSITIONS

1943-44	Surgical Intern, Peter Bent Brigham Hospital
1944-45	Assistant Resident Surgeon, Peter Bent Brigham Hospital
1944-45/1946-48	Assistant in Surgery, Harvard Medical School
1946-47	Assistant Resident Surgeon, Peter Bent Brigham Hospital
1948-50	Harvey Cushing Fellow, Harvard Medical School
1950-51	Chief Resident Surgeon, Peter Bent Brigham Hospital
1950-55	Instructor in Surgery, Harvard Medical School
1951-56	Director, Laboratory for Surgical Research, Harvard Medical School
1951-52	Henry E. Warren Fellow in Surgery, Harvard Medical School
1951-55	Junior Associate in Surgery, Peter Bent Brigham Hospital
1955-56	Associate in Surgery, Peter Bent Brigham Hospital
1955-56	Assistant Professor in Surgery Director, Laboratory for Surgical Research, Harvard Medical School
	Stuart McGuire Professor of Surgery, Chairman
	Department of Surgery, Medical College of Virginia
	Division of Virginia Commonwealth University

PROFESSIONAL SOCIETIES

A.A.A.S.
American College of Surgeons
American Medical Association
American Society of Clinical Investigation
American Society of Experimental Pathology
American Surgical Association
Boston Surgical Society

Endocrine Society
Halsted Society
International Congress-Nephrology
International Transplantation Society
New York Academy of Science
Pan American Surgical Society
Richmond Academy of Medicine
Richmond Surgical Society
Society of Experimental Biology and Medicine
Society of University Surgeons
Southern Surgical Association
Surgical Biology Club
The Society for Vascular Surgery
Society of Clinical Surgery
Virginia Medical Society
Virginia Surgical Society
Society of Surgical Chairmen
Naval Medical Research
Veterans Administration Advisory Group, Renal Transplants

AWARDS

1952-53/1955-56	Scholar in Cancer Research, American Cancer Society
1962	Francis Amory Prize (co-recipient) American Academy of Arts and Sciences (for developing technique of renal homotransplantation in man)
1968	Outstanding Harvard Alumnus of the State of Virginia
1969	Harvey Lecturer 1969 (The Immunological Consequences of Organ Homotransplantation)
1970	Valentine Award (co-recipient) New York Academy of Medicine for development of renal homotransplantation in man.
1971	Hadassah Humanitarian Award, Richmond Hadassah
1972	Distinguished Achievement Award from Modern Medicine Magazine

COUNCIL AND ADVISORY COMMITTEE MEMBERSHIPS

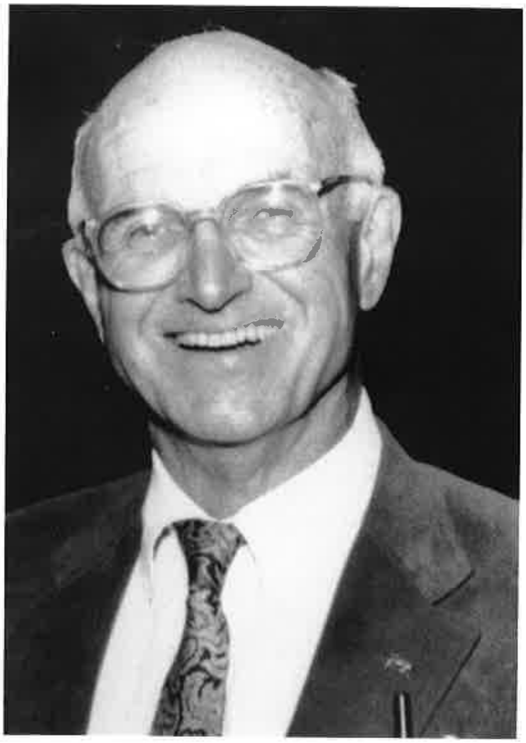
National Heart Institute, Program Project Committee
National Institutes of Health, Nephrology Planning Committee
Atomic Energy Commission Advisory Board
National Kidney Foundation, Task Force Committee
National Institutes of Health, Surgery Study Section

NOBEL PRIZE LECTURE: THE FIRST SUCCESSFUL TRANSPLANTS IN MAN

Joseph E. Murray

Address: Brigham and Women's Hospital
75 Francis Street
Boston, Massachusetts 02115

Joseph E. Murray



NOBEL PRIZE LECTURE: THE FIRST SUCCESSFUL ORGAN TRANSPLANTS IN MAN *

Joseph E. Murray

Preface

"If gold medals and prizes were awarded to institutions instead of individuals, the Peter Bent Brigham Hospital of 30 years ago would have qualified. The ruling board and administrative structure of that hospital did not falter in their support of the quixotic objective of treating end-stage renal disease despite a long list of tragic failures that resulted from these early efforts - leavened only by occasional encouraging notations such as those in the identical twin case. Those who were there at the time have credited Dr. George Thorn, Chairman of Medicine and Dr. Francis D. Moore, Chairman of Surgery, with the qualities of leadership, creativity, courage, and unselfishness that made the Peter Bent Brigham Hospital a unique world resource for that moment of history. (1)"

Introduction

Although renal transplantation had been performed sporadically during the first half of this century (2,3), planned programs for human organ transplantation started only in the late 1940s. At that time clinicians in Paris, London, Edinburgh, and Boston began renal transplantation in unmodified human recipients in spite of the warnings and pessimistic predictions of the many scientists and experienced clinicians.

Many bio-scientists had difficulty understanding the determined optimism of clinicians who were willing to evaluate any type of treatment which might possibly help these terminally ill uremic patients, most of whom were young and otherwise healthy. Tantalizing reports of functioning human renal transplants had surfaced from time to time (4-6); these hints of success were further encouragement.

In this lecture I will focus on the renal transplant program of the Peter Bent Brigham Hospital (now the Brigham and Women's Hospital) in Boston and explain how this small hospital became involved in transplantation. The medical and surgical services, along with the Department of Pathology under Dr. Gustave J. Dammin, led the way and ultimately renal transplantation involved most of the hospital in some way or other.

The full story of successful organ transplantation in man weaves together three separate pathways: the study of renal disease, skin grafting in twins, and surgical determination. A leitmotif permeates each of these pathways, ie, a single event or report was critical for medical progress.

Renal Disease

The first two Physicians-in-Chief, the Hersey Professor at Harvard in their day, Dr. Henry Christian and Dr. Soma Weiss, had a major interest in renal disease. When Dr. Thorn succeeded Dr. Weiss in 1943 he and his associate Dr. James O'Hare continued this interest, especially the relationship of renal disease to hypertension. After World War II Dr. Thorn invited Dr. Willem Kolff from The Netherlands to Boston to demonstrate a dialysis machine which he had developed during his forced confinement by the Germans. Dr. Carl W. Walter helped to improve the design and thus the Kolff-Brigham "artificial kidney" was devised. It was first used in patients in 1948 and set the stage for extensive new innovative approaches to both acute reversible renal disease and end-stage failure.

---

* © The Nobel Foundation 1991

Because renal dialysis provided only temporary improvement for the patient, it was logical to seek a more permanent therapy. (Chronic dialysis was not developed until 10 years later by Schribner in Seattle). In the late 1940s during Grand Rounds at the Brigham, I was astounded to hear Dr. Thorn say, "The best way to treat hypertension is to remove both kidneys!" The entire audience gasped. The seed for the Brigham renal transplant program had been planted.

Skin Grafting in Twins

This thread in the story involves the biological phenomena of monozygotic and dizygotic twinning. The monozygotic, "identical" twin experience starts with the treatment of burns, the dizygotic, "nonidentical" twin story begins with freemartin cattle (the spelling varies: one word, two words, or hyphenated).

In 1932 Dr. E. Padgett of Kansas City reported the use of skin allografts from family and unrelated donors to cover severely burned patients who had insufficient unburned donor sites for the harvesting of autografts. Although none of these skin allografts survived permanently, many would remain long enough to control infection and fluid loss and thus gain time for the donor sites to reepithelialize. It was difficult to determine accurately the duration of survival of any one allograft; some seemed to melt away slowly and be replaced by adjacent skin, others seemed to be rejected rapidly (7).

Skin grafts from family members seemed to survive longer than those from unrelated donors. But even after observing hundreds of skin allografts, one could not be certain about their survival time. One certainty was established when Dr. J.B. Brown of St. Louis in 1937 achieved permanent survival of skin grafts exchanged between monozygotic twins (8).

This single observation, although restricted in application, was the only ray of light in the problem of tissue and organ replacement until Gibson and Medawar demonstrated that a second allograft from the same donor was rejected more rapidly than the first (9). This clear description of the "second set" phenomenon established that the rejection process was not immutable; instead it implied an allergic or immunological process which potentially might be manipulated.

The dizygotic twin story starts with John Hunter's description of freemartin cattle in 1779 (10). Freemartins are twin cattle in which the male is normal and the female sterile. Hunter cites Roman descriptions of the phenomenon and then described the physical characteristics of several pairs he had collected in England.

The trail does not appear again until 1917 when Lillie, not content with mere descriptions, dissected the placentae of several pairs of freemartin cattle and noted the placental intermingling of blood between these differently sexed twins (11). Thirty years elapsed before Owen published on the tolerogenic consequences of this placental intermingling of circulation (12). Following this Anderson in 1949 reported successful skin allografts between the freemartin and the normal male (13).

The freemartin story culminates in the report of Billingham, Brent and Medawar describing an acquired immunological tolerance produced by neonatal injection of donor cells into a future allograft recipient (14). They indicate that it was the experimental counterpart to Owen's naturally occurring model. Although not applicable to the clinical situation, their experimental breeching of the immunological barrier was another impetus for optimism in the problem so many considered hopeless.

Sir Michael Woodruff, the pioneer transplant surgeon in Edinburgh, confirmed the freemartin concept in man when he found a pair of twins, one male the other female, who shared elements of different red cell types. Postulating a shared placental circulation between the two, he cross skin grafted them successfully (15).

Surgical Determination

In 1912, Dr. A. Carrel received a Nobel Prize "in recognition of his work on vascular suture and the transplantation of blood vessels and organs." He clearly recognized the difference in the survival times between autografts and allografts in experimental animals, but he did not conceptualize rejection as distinct from other graft-destroying processes.

Quinby in 1916 used the canine renal autograft model to study the effect of denervation on renal function (16). Mann and Williamson a decade later noted the different survival times between canine renal autografts and allografts (17,18), but like Carrel, they did not pursue the long-term fate of the autografts. After World War II Dempster (19) and Simonsen (20) published extensively on canine renal transplantation concentrating on the biology and biochemistry of allograft rejection. They demonstrated that skin and kidney allografts possess a common antigen which could sensitize a recipient to a subsequent allograft of either tissue from the same donor. In these reports, there was the tacit assumption that renal autograft function would deteriorate ultimately, possibly because of lack of nerve supply and/or lymphatics.

From a physiological view, if human renal transplantation were to be successful, we needed to establish that renal transplants in the absence of an immunological barrier could function permanently. In the course of many laboratory experiments on canine renal transplantation, I had developed a reproducible operation using intra-abdominal vascular anastomoses and a uretero-cystostomy for urinary drainage, placing the kidney in the lower abdomen. This has become the universal renal transplant procedure since that time. Complete functional studies of some of these autografted kidneys two years after transplantation proved them to be completely normal (21).

Dr. Murray with the dogs that received kidney transplants before the operation was given to humans.

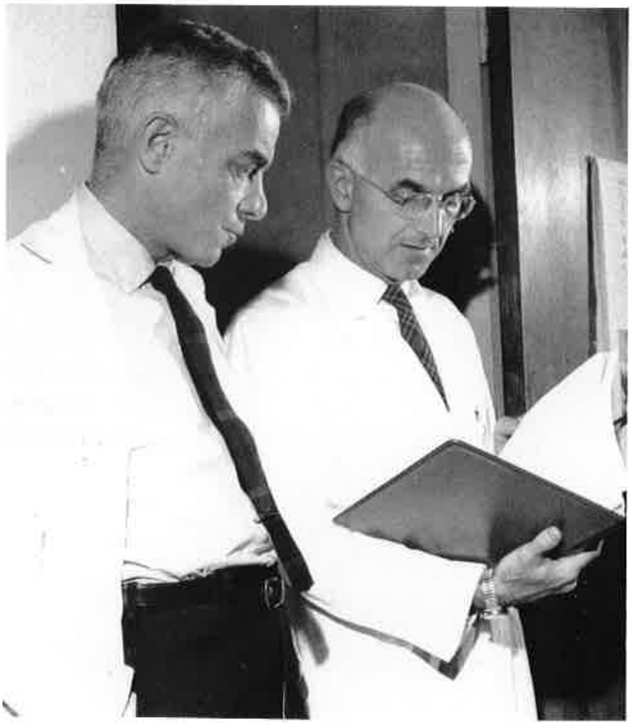
The Three Trails Merge

These three trails merged at the Peter Bent Brigham in the late 1940s. All the elements for a sound renal transplant program were in order: experienced knowledge in renal disease, availability of dialysis, and skilled imaginative surgeons. To minimize morbidity, the first allografts in these unmodified human recipients were added as a third kidney in the thigh under local anesthesia. Dr. David Hume was the surgeon for these patients and he anastomosed the renal vessels of the graft to the femoral vessels of the recipient. Urine was collected in a bag from a skin ureterostomy (22).

Several of these unmodified human allografts functioned better than experimental canine allografts would have predicted. Possible explanations were an immunosuppressive effect of uremia or a beneficial effect of acute tubular necrosis which occurred regularly in these inadequately preserved donor kidneys. One thigh transplant functioned for almost six months with return of the patient's biochemical profile and blood pressure to normal, demonstrating that transplants could rectify the pathophysiologic disorder of renal insufficiency.

The very first renal transplant in 1945 at the Brigham deserves special comment. The patient was a young woman in renal failure following obstetrical complications. The purpose of the transplant was to provide temporary renal function until her own kidneys recovered from acute tubular necrosis. Dr. Thorn recalls his inability to obtain permission to have the patient transferred to a regular operating room (this was prior to Dr. Moore's tenure) so the operation was performed on the old E-Second Ward by Dr. Charles Hufnagel, then a Research Fellow working on vascular grafts, Dr. Earnest Landsteiner, then Chief Resident in Urology, and Dr. David Hume, then Assistant Resident in Surgery. The donor kidney was anastomosed in the antecubital space under local anesthesia using a cutaneous ureterostomy.

According to Dr. Robert J. Glaser, who was Assistant Resident on the medical service at that time, "secretion of urine was minimal, and certainly did not, ‘rescue the woman from her crisis.’ The kidney functioned poorly and only transiently, and the patient continued to have a stormy course, although fortunately, despite our lack of understanding at the time of how best to treat renal shutdown, she ultimately did respond



Dr. Merrill and Dr. Murray on their rounds.

and she left the hospital with normal renal function and in good health."

Dr. Glaser further reports that her happy state was short-lived because she died a few months later of fulminating hepatitis secondary to pooled plasma infusions which she had received in the course of her treatment. Interestingly, Dr. Glaser still recalls taking care of the patient whose kidney was ultimately used as the donor transplant. "The patient had disseminated lupus erythematosus and had been in the Brigham many times. Although in patients with advanced lupus the kidney is usually badly damaged, in this particular case renal manifestations were relatively limited, and when her kidney became available it was therefore used (23)."

The Identical-Twin Patient

In the fall of 1954, Dr. Donald Miller of the United States Public Health Service telephoned Dr. Merrill in order to refer a patient with severe renal disease. Moreover, Dr. Miller suggested there might be the opportunity for transplantation of a kidney because the patient had a healthy twin brother. Needless to say, the transplant team was interested in the possibility of transplanting a genetically compatible kidney. Cross skin grafting established genetic identity, renal disease was brought under control with medications and dialysis, and we were ready to apply our laboratory-tested surgical technique to man.

The only remaining problem was the ethical decision concerning the removal of a healthy organ from a normal person for the benefit of someone else. For the first time in medical history a normal healthy person was to be subjected to a major surgical operation not for his own benefit.

After many consultations with experienced physicians within and outside the Brigham and with clergy of all denominations, we felt it reasonable to offer the operations to the recipient, the donor, and their family. We discussed in detail the preparations, anesthesia, operations, possible complications, and anticipated result.

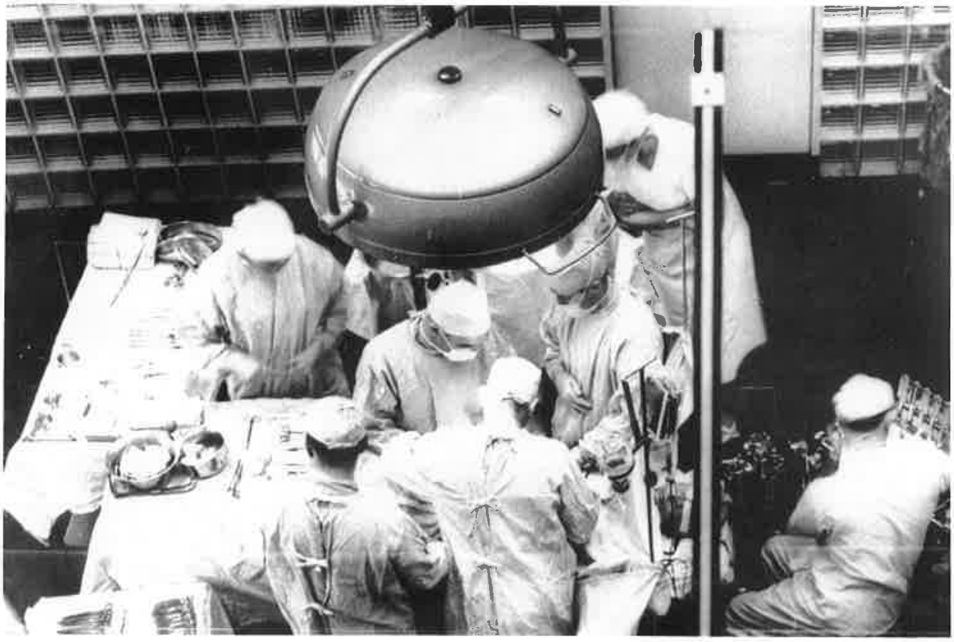
At the conclusion of our last preoperative discussion, the donor asked whether the hospital would be responsible for his health care for the rest of his life if he decided to donate his kidney. Dr. Harrison, the surgeon for the donor, said, "Of course not." But he immediately followed with the question, "Ronald, do you think anyone in this room would ever refuse to take care of you if you needed help?" Ronald paused, and then understood that his future depended upon our sense of professional responsibility rather than on legal assurances.

Once the patients and the team decide to proceed with the transplant, an extra professional burden falls on the surgeon performing the donor nephrectomy because his patient is expected to survive normally. In contrast, the surgeon performing the transplant is operating on a patient otherwise doomed to die, and the nephrologist caring for these critically ill patients cannot be faulted for failure to cure.

Postoperatively the transplanted kidney functioned immediately with a dramatic improvement in the patient's renal and cardiopulmonary status. This spectacular success was a clear demonstration that organ transplantation could be life saving. In a way, it was spying into the future because we had achieved our long-term goal by bypassing, but not solving, the issue of biological incompatibility (24,25).

Subsequent Laboratory and Clinical Study

The impact was worldwide and stimulated widespread laboratory attempts to breech the immunological barrier. Experimental protocols included total body X-ray treatment followed by marrow infusion, immunoparalysis by consecutive graftings,



The world's first organ transplant (1954). The donor and recipient were identical twins.

immunological enhancement or adaptation by prior exposure of the host or graft to antigen, matching of donor and recipient by red or white cell typing, and the use of drugs such as toluene and nitrogen mustard.

We continued with both clinical and laboratory studies. In a series of volunteer uremic patients, we noted a prolonged but not permanent survival of skin allografts, suggesting the uremic state itself was immunosuppressive (26). In several series of dogs we tried without success to establish a state of renal insuffiency by partial removal of renal mass, infusion of toxins directly into the renal artery, temporary ischemia, and/or thermal insult. Attempts to prolong graft survival by treating the host with steroids and/or anticoagulants also failed (27).

To study the "X-ray marrow" protocol, which seemed to have the best potential for human application, we used mice and rabbits. Using sublethal or lethal doses of total body X-ray, followed by marrow infusions from single or multiple donors, we were able to obtain a limited number of long-surviving skin allografts (28).

Simultaneously during the 1950s we transplanted several more sets of identical twins. One twin transplanted in 1956 completed a pregnancy two years later (29). She is now a grandmother and the longest-living renal transplant recipient. Her donor, also a grandmother, likewise is in perfect health. Initially regarded as a unique occurrence, the identical twin situation has continued to reappear worldwide. It is estimated that at least 50 patients have now received transplants from their identical twins.

Several patients were referred during these years suffering from accidental loss of a solitary kidney. Because we had obtained limited encouraging laboratory results, it seemed reasonable to treat some of these patients with an "X-ray-marrow" protocol, ie, total body X-ray followed by marrow infusion and a renal allograft. In most of the patients, the transplanted kidneys functioned immediately and continued to do so for several weeks, but in only one of 12 patients did function persist beyond three months.

The one success was our third patient, a dizygotic twin who received a sublethal,

Press conference in 1959 at the Peter Bent Brigham Hospital on the occasion of the first successful kidney allograft.

non-marrow-requiring, dose of total body X-ray, given by Dr. James B. Dealy, followed by a kidney graft from his twin brother in 1959. He recovered after a difficult complicated postoperative course; he subsequently led a full active normal life until he died of cardiac problems 25 years later. He was the world's first successful fraternal-twin renal allograft and was the enticement and stimulus for us to continue this method of procedure until drugs became available (30-32). The Hamburger group in Paris subsequently had a similar success with a dizygotic twin recipient following sublethal X-ray treatment.

The First Successful Cadaveric Transplant in Man

Although we began our first experiments in rabbits using Thio-TEPA as a substitute for total body X-ray treatment in 1958 (33), the real breakthrough came with the introduction of immunosuppressive drugs by Schwartz and Dameshek in 1959 (34). They prevented rabbits from producing antibody against human serum albumin by treating them for two weeks with the antimetabolite, 6-mercaptopurine. This "drug-induced tolerance" remained after drug treatment was stopped, even though the animals could react normally against another protein antigen, bovine gamma globulin. Thus the tolerance seemed to be specific for an antigen introduced at the time of drug administration. Roy Calne in London (35) and Charles Zukoski in Virginia (36) tested this drug in the canine renal transplant model and had encouraging results.

On the advice of Sir Peter Medawar, in 1960 Calne came to Boston to work with me in Dr. Francis D. Moore's Department at the Harvard Medical School and the Peter Bent Brigham Hospital. Calne introduced us to Dr. Hitchings and Dr. Elion of the Burroughs-Wellcome Laboratories who became enthusiastic collaborators. Following Calne's arrival and with the use of drugs supplied by Dr. Hitchings the improvement in allograft survival was rapid and dramatic. Soon we had many bilaterally nephrectomized dogs in our laboratory living on solitary renal allografts. Some survived for months, eventually for years. One produced a normal litter sired by a drug-treated allografted male. One dog recovered from a severe osteomyelitis of the mandible, indicating he was not an immunological cripple, a state we feared might result from prolonged use of the drugs (37). During this time we were testing other drugs from Hitchings and Elion, who were frequent visitors and knew most of our dogs by name. The experimental drug, BW-322, the imidazole derivative of 6-mercaptopurine, seemed to have the best therapeutic index. This drug is now known as azathioprine, or Imuran, and was used throughout the world to support organ transplantation for 20 years. Now newer drugs are available and under study to extend their usefulness and diminish toxicity.

Reassured by these results, we decided to use these drugs in humans for immunosuppression. The first renal transplant recipient to receive azathioprine was an adult transplanted with an unrelated kidney in March 1961. The transplant functioned well for over one month, but the patient died of drug toxicity because the dosage required in dogs was toxic for man.

Our second patient also died of drug toxicity even though we halved the dose used for our first patient. For the first time in our experience we were able to reverse the rejection process. When we discontinued the drug because of leucopenia, rejection started to occur. As his leucopenia improved, we restarted the drug which reversed the rejection process and his renal function improved. Nevertheless he did succumb to sepsis after a month (38).

Our third patient, transplanted in April 1962, was treated with azathioprine following a cadaveric renal allograft. He survived over one year and was the world's first suc-

With Sir Roy and Patsy Calne on Cape Poge, Martha's Vineyard, 1980.

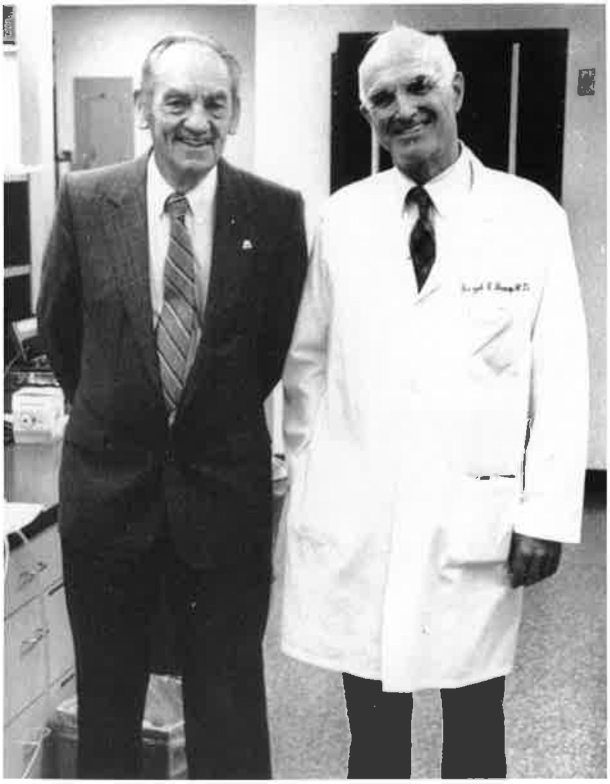
cessful unrelated renal allograft. We reported these results in the *New England Journal of Medicine* (39) and a case report in the *Journal of the American Medical Association* followed (40). Dr. Willard Goodwin, at the University of California in Los Angeles, almost immediately introduced the use of corticosteroids as a further adjunct to the treatment (41). Subsequently several transplantation groups worldwide began their own productive transplantation programs.

By 1965, one-year survival rates of allografted kidneys from living related donors were approaching 80 percent and from cadavers 65 percent. Regional and national donor procurement programs were established along with an International Renal Transplant Registry (42). Optimism and enthusiasm were high as new drugs and other methods of immune suppression were tested along with refinements in tissue typing and improved organ preservation. Antilymphocyte serum and globulin prepared in horse, sheep, and rabbit along with thoracic duct drainage of lymphocytes were among the more promising regimens tested. Currently it is estimated that more than 200,000 human renal transplants have been performed worldwide.

Other Organs

The success with renal allografts naturally led to attempts to transplant other organs. Moore developed the surgical technique for orthotopic canine liver transplantation (43), the model procedure used by Starzl for first successful human liver allografts (44). Calne, returning to Cambridge, England, also developed an extensive human liver transplantation experience. For almost 15 years Starzl and Calne performed the vast majority of the world's human liver transplants (45). Today the operation is second only to kidney in frequency and is performed universally .

The next organ to be transplanted was the heart. Lower and Shumway had developed the surgical technique in dogs in 1961 and were planning a careful program for cardiac transplantation in humans. After Barnard's first human cardiac transplant in 1967, many other cardiac surgeons with little or no immunological background rapidly accumulated large numbers of heart-



George Hitchings and Joe Murray at the dedication of the Hitchings-Murray Laboratory at the Brigham and Women's Hospital, 1984.

transplanted patients, only to witness them all die of rejection within a few months. This period between 1968 to 1970 was undoubtedly transplantation's darkest hour. The sole redeeming feature in heart transplantation was the continuation of Shumway's program at Stanford which achieved permanent success in 1970 (46). Today with the development of newer drugs, cardiac transplantation is a recognized and accepted form of treatment.

Single- and double-lung transplantation have followed, as well as combined heart-lung transplants. Transplantation of the pancreas, with or without an accompanying renal graft, is commonly done. Multiple organ transplants in combination with liver and parts of the intestinal tract have also been successful. In 1989, there were 8,890 kidney, 2,160 liver, 1,673 heart, 413 pancreas, and 67 heart-lung transplants performed in the United States alone (47).

Ironically, allografts of skin, the tissue used classically in most of the early studies of transplantation, have proven to be the most difficult to transplant. Skin is the ultimate protection of the individual against the environment and therefore over the ages has evolved into our strongest barrier against foreign proteins. The earlier conventional wisdom was that the fate of skin allografts predicted the results of other transplants. Commenting on the contrasting survival rates of skin and kidney allografts in immunosuppressed dogs, Medawar proclaimed with his customary flair, that the success of organ transplantation has "overthrown the doctrinal tyranny of skin grafts (48)."

The Future

Although thousands of young lives have already been saved by the use of various immunosuppressive regimens, serious complications still occur as a result of the treatment. The ultimate aim is to achieve an immunological tolerance between donor and recipient, eliminating entirely the need for drugs. There are hints both in the laboratory (49) and in man (50) that the liver itself can produce tolerogenic factors which may reduce or eliminate the need for immunosuppressive drugs. Discovering or uncovering naturally occurring immunosuppressive substances seems likely. It surely is as probable as the prospect of obtaining successful organ transplants was 45 years ago.

REFERENCES

1. Starzl TE. The landmark identical twin case. JAMA 1984; 251:2572.
2. Moore FD. Transplant, The Give and Take of Tissue Transplantation. Simon and Schuster, New York, 1972; 66.
3. Groth CE. Collective review. Landmarks in clinical renal transplantation. Surg Gynecol Obstet 1972; 134:323.
4. Lawlor RH, West JW, McNulty PH, et al. Homotransplantation of the kidney in the human: supplemental report of a case. JAMA 1951; 147:45.
5. Kuss R, Teinturier J, Milliez P. Quelques essais de greffe du rein chez l'homme. Mem Acad Chir 1951; 77:755.
6. Michon L, Hamburger J, Economos N, et al. Une tentative de transplantation renale chez l'homme: aspects medicolaux et biologiques. Presse Med 1953; 61:1419.
7. Padgett EC. Is iso-skin grafting practicable? South Med J 1932; 25:895.
8. Brown JB. Homografting of skin: with report of success in identical twins. Surgery 1937; 1:558.

9. Gibson T, Medawar PB. Fate of skin homografts in man. J Anat 1942; 77:299.

10. Hunter J. On the free martin. R Coll Surg XX; Feb. 25, 1779.

11. Lillie FR. The theory of the free-martin. Science 1916; 43:611.

12. Owen RD. Immunogenetic consequences of vascular anastomoses between bovine twins. Science 1945; 102:400.

13. Anderson D, Billingham RE, Lamkin GH, et al. Use of skin grafting to distinguish between monzygotic and dizygotic twins in cattle. Heredity 1951; 5:379

14. Billingham RE, Brent L, Medawar PB. Actively acquired tolerance of foreign cells. Nature 1953; 172:603.

15. Woodruff MFA, Lennox B. Reciprocal skin grafts in a pair of twins showing blood chimerism. Lancet 1959; 2:476.

16. Quinby WC. The function of the kidney when deprived of its nerves. J Exp Med 1916; 23:535.

17. Williamson CS. Further studies on the transplantation of the kidney. J Urol 1926; 16:231.

18. Sterioff S, Rucker-Johnson N. Frank C. Mann and transplantation at the Mayo Clinic. Mayo Clin Proc 1987; 62:1051.

19. Dempster WJ. The homotransplantation of kidneys in dogs. Br J Surg 1953; 40:477.

20. Simonsen M, Buemann J, Gammeltoft A, et al. Biological incompatibilty in kidney transplantation in dogs. Acta Pathol Microbiol Scand 1953; 32:1.

21. Murray JE, Lang S, Miller BJ, et al. Prolonged functional survival of renal autografts in the dog. Surg Gynecol Obstet 1956; 103:15.

22. Hume DM, Merrill JP, Miller BF, et al. Experiences with renal homotransplantation in the human: report of nine cases. J Clin Invest 1955; 34:327.

23. Glaser RJ. Footnotes to kidney transplant history. Focus: March 31, 1968. Harvard University News Office for the Medical Area, Boston, 1968; 8.

24. Murray JE, Merrill JP, Harrison JH. Renal homotransplantation in identical twins. Surg Forum 1955; 6:432.

25. Merrill JP, Murray JE, Harrison JH, et al. Successful homotransplantation of the human kidney between identical twins. JAMA 1956; 160:277.

26. Dammin GJ, Couch NP, Murray JE. Prolonged survival of skin homografts in uremic patients. Ann NY Acad Sci 1957; 64:967.

27. Lang S, Murray JE, Miller BF. Homotransplantation of ischemic kidneys into dogs with experimentally produced impairment of renal function. Plast Reconstr Surg 1956; 17:211.

28. Wilson RE, Dealy JB, Sadowsky N, et al. Transplantation of homologous bone marrow and skin from common multiple donors following total body irradiation. Surgery 1959; 46:261.

29. Murray JE, Merrill JP, Harrison JH. Kidney transplantation between seven pairs of identical twins. Ann Surg 1958; 148:343.

30. Murray JE, Merrill JP, Dammin GJ, et al. Study of transplantation immunity after total body irradiation: clinical and experimental investigation. Surgery 1960; 48:272.

31. Merrill JP, Murray JE, Harrison JH, et al. Successful homotransplantation of the kidney between non-identical twins. N Engl J Med 1960; 262:1251.

32. Murray JE, Merrill JP, Dammin GJ, et al. Kidney transplantation in modified recipients. Ann Surg 1962; 156:337.

33. Porter KA, Murray JE. Homologous marrow transplantation in rabbits after triethylenethiophosphoramide (Thio-TEPA). AMA Arch Surg 1958; 76:908.

34. Schwartz R, Dameshek W. Drug-induced immunological tolerance. Nature 1959; 183:1682.

35. Calne RY. The inhibition of renal homograft rejection in dogs by 6-mercaptopurine. Lancet 1960; 1:417.

36. Zukoski C, Lee HM, Hume DM. The prolongation of functional survival of canine renal homografts by 6-mercaptopurine. Surg Forum 1960; 11:470.

37. Calne RY, Alexandre GPJ, Murray JE. A study of the effects of drugs in prolonging survival of homologous renal transplants in dogs. Ann NY Acad Sci 1962; 99:743.

38. Murray JE, Balankura O, Greenburg JB, et al. Reversibility of the kidney homograft reaction by retransplantation and drug therapy. Ann NY Acad Sci 1962; 99:768.

39. Murray JE, Merrill JP, Harrison JH, et al. Prolonged survival of human-kidney homografts by immunosuppressive drug therapy. N Engl J Med 1963; 268:1315.

40. Merrill JP, Murray JE, Takacs F. Successful transplantation of kidney from a human cadaver. JAMA 1963; 185:347.

41. Goodwin WE, Kaufman JJ, Mims MM, et al. Human and renal transplantation. I. Clinical experiences with six cases of renal transplantation. J Urol 1963; 89:13.

42. Murray JE, Barnes BA, Atkinson JC. Fifth report of the human kidney transplant registry. Transplantation 1967; 5:752.

43. Moore FD, Smith LL, Burnap TK, et al. One stage homotransplantation of the liver following total hepatectomy in dogs. Transplant Bull 1959; 6:103.

44. Starzl TE, Groth CG, Brettschneider L, et al. Orthotopic transplantation of the human liver. Ann Surg 1968; 168:392.

45. Calne RC, Williams R. Liver transplantation in man. I. Observations on technique and organization in five cases. Br Med J 1968; 4:535.

46. Dong E, Griepp RB, Stinson EB, et al. Clinical transplantation of the heart. Ann Surg 1972; 176:503.

47. U.S. Dept of Health and Human Services, Division of Organ Transplantation, Rockville, MD.

48. Medawar PB. Transplantation of tissues and organs: introduction. Br Med J 1965; 21:97.

49. Calne RY, Sells RA, Pena JR, et al. Induction of immunological tolerance by porcine liver grafts. Nature 1969; 223:472.

50. Davies DR, Pollard SG, Calne RY. Forum on immune suppression: Hellenic Transplantation Society. Athens, Greece, 1990.

ANNOTATIONS FOR REFERENCES

2. This book provides detailed background of the earliest attempts in human renal transplantation from around the world, as well as personalized documentation along the way. The various activities within the Peter Bent Brigham Hospital are detailed in a lively informative way.

3. This excellent collective review pays particular attention to the period from 1950 to 1965, but also documents the unsuccessful attempts in the first half of this century.

4. Originally proclaimed as a "success", this report excited much publicity. However, there was no solid evidence of transplant function.

When the patient died a few years later, only scar tissue was found at the site of the transplant.

5,6. These two dedicated French groups, working independently, obtained definite evidence of transient renal transplant function in several patients. We all were in frequent communication with each other and shared the optimism that the problem eventually would prove soluble.

7. The title of this report incorrectly uses the term "isografting." This indicates the confusion in terminology which existed at the time. Several titles of ours cited in this bibliography are imprecise. The concise terms "autograft," "isograft," "allograft," and "heterograft" were not established for universal usage until 1960 by Peter Gorer.

8. Brown, who had observed Padgett's patients, was never certain about the fate of any allografts used in burned patients. That is why subsequently he sought out a pair of identical twins to test with reciprocal skin grafts. These were true "isografts," ie, grafts between genetically identical members of the same species, similar to grafts between genetically pure strains of mice.

Brown, from Washington University in St. Louis, was undoubtedly influenced by Leo Loeb of the same institution. Loeb had written a book entitled *The Basis of Individuality* in which he categorically stated that grafts between individual humans would never be possible because individual differences existed even at the cellular level.

Brown was Chief of Plastic Surgery at Valley Forge General Hospital, Pennsylvania, the hospital to which I was randomly assigned during World War II. We often discussed the biology of transplantation while scrubbing and operating.

10. Dr. Emile Holman and Dr. Brown both had noted and written that second skin grafts from the same donor "seemed" to disappear more rapidly than the first. But they had not recognized or formulated an underlying principle on which others could build.

11. In this same issue of *Science* there is another report describing over 300 freemartin pairs without adding any new information or findings. Lillie, on the other hand, had rolled up his sleeves and dissected a few of these cattle and discovered the intermingling of placental blood vessels. Incidently, Lillie was one of the founders of the Marine Biological Laboratory at Wood's Hole, Massachusetts, and for years served as its Director.

12. Owen's work, funded by the American Guernsey Association, was part of a study of the freemartin, whose birth could be a major financial burden for an individual dairy farmer.

14. Carrel received the Nobel Prize in 1912. Medawar, together with Sir Frank MacFarlane Burnett, received the Nobel Prize in 1960 for "the discovery of acquired immunological tolerance." Others receiving the Nobel Prize in areas related to transplantation are Baruj Benacerraf, Jean Dausset, and George Snell, in 1980, "for their discoveries concerning genetically determined structures on the cell surface that regulate immunological reactions," and George

Hitchings and Gertrude Elion, in 1988, "for their discoveries of 'important principles for drug treatment.'"

19,20. Dempster and Simonsen were imaginative and productive investigators who added much to our understanding of transplantation biology and particularly to the rejection of renal grafts. Simonsen later performed a successful renal graft between freemartin cattle.

23,24. Dr. Merrill and I, as respective heads of the medical and surgical portions of the Brigham transplant program, decided that, for publications generally, I would present our patients in groups as series and he as individual case reports.

31. This watershed report of the Brigham experience is our final report on the use of total body X-radiation in our 12 patients and also includes our first six patients treated with immunosuppressive drugs. In addition, it includes experiments in dogs, selectin from over 300 transplants performed within two years, which demonstrated not only prolonged survival of the allografts, but also the specificity of the drug-induced tolerance. These long-term surviving dogs were capable of rejecting skin allografts from the third-party donors, as well as skin from the kidney donor if the skin graft was placed after the renal graft was well established. For a more complete "Analysis of Mechanism of Immunosuppressive Drugs in Renal Transplantation," cf. Annals of Surgery, 160: 449, 1964. For follow-up on the subsequent Brigham experience in clinical renal transplantation, cf. Annals of Surgery, 184: 565, 1976; "Renal Transplantation - A Twenty-five Year Experience," Murray, J.E., Tilney, N.L., and Wilson, R.E.

37. This report is a direct outgrowth of the earlier renal perfusion studies of Dr. Nathan Couch. After demonstrating postperfusion viability of an extra-corporeally perfused kidney, he attempted to alter its antigenicity by perfusing it with blood components from a future recipient. After observing several unsuccessful attempts, Dr. David Hume suggested that we use the future recipient dog itself as the pump because it would eliminate the problems both of the pump and the perfusate. Following this suggestion, we found that by attaching the extra-corporeal kidney to a prospective recipient by means of canulae, we were able to initiate the rejection process within a day or two. But, if we reconnected the rejecting kidney to its original owner in time, the rejection process could be reversed.

43. This reports the first successful human organ transplant other than the kidney. In the discussion Dr. Moore says, "This is a magnificent achievement, and liver surgery as of this day has an entirely new look from hither forward." Reflecting on this remarkable contribution of Starzl's, it is important to recall that his success did not come easily. It was preceded by years of disappointment and discouragement, and success resulted only from his persistant logical dedication to the project.

46. Shumway, like Starzl, achieved success only by persistence and dedication. Neither aimed for the spectacular "overnight" break-

through; both realized that solid progress requires time, basic knowledge, and unselfish teamwork.

49. Although Calne reported more than 25 years ago that the liver might possess an intrinsic immunosuppressive factor, it has been dismissed as an idiosyncrasy of the pig and not relevant for man. However, there are emerging impressions from the simultaneous transplantation of multiple organs in man that the presence of a liver allograft seems to improve the survival of the accompanying allografts. This seems to apply especially for intestinal transplants.

CURRICULUM VITAE

Joseph E. Murray

PERSONAL

Born: April 1, 1919; Milford, Massachusetts
Home Address: 108 Abbot Road
Wellesley Hills, Massachusetts 02181
Office Address: Brigham and Women's Hospital
75 Francis Street
Boston, Massachusetts 02115

EDUCATION

1940	College of the Holy Cross, Worcester, Massachusetts, A.B.
1943	Harvard Medical School, M.D.
1944	Surgical Intern, Peter Bent Brigham Hospital, Boston, Massachusetts
1947-50	Assistant Resident in Surgery, Peter Bent Brigham Hospital
1951	Resident in Plastic Surgery, The New York Hospital
1956-66	Director, Laboratory for Surgical Research, Harvard Medical School and the Peter Bent Brigham Hospital

BOARD CERTIFICATION

1952	Certified, General Surgery
1954	Certified, Plastic Surgery

MILITARY SERVICE

1944-47	Major, M.C.Army of the United States, Valley Forge General Hospital Pennsylvania

POSITIONS

1962	Assistant Clinical Professor of Surgery, Harvard Medical School
1965	Lecturer, Royal College of Surgeons of Canada
1967	Associate Clinical Professor of Surgery, Harvard Medical School
1969	Visiting Professor of Plastic Surgery, General Surgery and Urology, University of California
1970	Professor of Surgery at the Peter Bent Brigham Hospital, Children's Hospital Medical Center, and Harvard Medical School
1974	Queen's University Hospital, Tehran, Iran

1974 Senior Associate in Surgery and Chief of Division of Plastic Surgery, Children's Hospital Medical Center

1975 Visiting Professor, Mayo Medical School, Rochester, Minnesota

1976 Visiting Professor, Baylor University Hospital, Dallas, Texas

1976 Queen's University Hospital, Tehran, Iran

1977 Hospital General, Mexico City, Mexico

1979 Educational Foundation of the American Society of Plastic and Reconstructive Surgeons, Travelling Professor

1980 First Greeley Lecturer, Chicago Surgical Society, Chicago, Illinois

1986 Doctor of Science (Honorary), Roger Williams College, Bristol, Rhode Island

PROFESSIONAL SOCIETIES

1954 Diplomat, American Board of Surgery

1975 President, Boston Surgical Society

American Association of Plastic Surgeons
  1964-65 President
  1987 Honorary Member

American Board of Plastic Surgery
  1954 Diplomat
  1964-70 Member of Board
  1969-70 Chairman

American Medical Association

American Society for Plastic and Reconstructive Surgeons

American Society for Surgery of the Hand

1978 First Vice President, American Surgical Association

American College of Surgeons
  Plastic Surgical Representative
  1954 Fellow
  1970-79 Forum Committee Regent
  1983-84 First Vice President

1983-84 First Vice President, American College of Surgeons

1983-84 President, Harvard Medical Alumni Association

1987 President, New England Surgical Society

American Association of Plastic Surgeons

Fellow, American College of Surgeons

1978/1986 Honorary, American Society of Transplant Surgeons

American Surgical Association

Society of University Surgeons

	Founding Member, Society of Head and Neck Surgeons
	Founding Member, Transplantation Society
	Charles River Medical Society
1980	Honorary Member, Chicago Surgical Society
1964-65	President, New England Society for Plastic and Reconstructive Surgery
1985	Honorary Fellowship, Royal Australian College of Surgeons
1987	Honorary Fellowship, Royal College of Surgeons of London
	Society of University Surgeons
1966-68	Councillor, Transplantation Society
	Massachusetts Medical Society

AWARDS

1962	Francis Amory Prize of the American Academy of Arts and Sciences Boston, Massachusetts
1963	Gold Medal of International Society of Surgeons, Brussels, Belgium
1969	Honorary Award of the American Association of Plastic Surgeons
1970	Ninth Ferdinand C. Valentine Medal and Award of the New York Academy of Medicine
1977	George B. Kunkel, M.D. Award, Harrisburg Hospital
1979	National Kidney Foundation Gift of Life Award
1980	VIII International Congress of Transplantation Society Dedication to Drs. Joseph E. Murray, John P. Merrill and Jean Hamburger
1980	Honorary Citizen's Award from the City of Boston on its 350th Anniversary
1981	Clinician of the Year, American Association of Plastic Surgeons, Williamsburg, Virginia
1985	Honorary Fellow, Royal Australasian College of Surgeons
1987	Honorary Award, The Boston Leadership Forum of Greater Boston Chamber of Commerce
1987	Honorary Fellow, Royal College of Surgeons of London
1988	Honorary Fellow, Royal College of Surgeons in Ireland
1990	Olof Af Acrel Medal, The Swedish Society of Medicine
1990	Nobel Prize in Medicine
1991	Medal for Distinguished Service to Surgery, American Surgical Association

COUNCIL AND ADVISORY COMMITTEE MEMBERSHIPS

	Founder, International Kidney Transplant Registry
	Member, Ad Hoc Committee, Harvard Medical School, to examine the definition of death
1956-59	National Research Council, Committee on Tissue Transplantation
1956-69	Member of the National Research Council Committee on Tissue Transplantation
1962-66	National Institute of Health, Surgical Studies
1962-66	Member of the National Institute of Health Surgical Studies Section
1963	Chairman, National Research Council, First Human Kidney Transplant Conference, Washington, D.C.
1963	National Research Council, Chairman, First Human Kidney Transplant Conference, Washington, D.C.
1965	National Research Council, Chairman, Second Human Kidney Transplant Conf., Washington, D.C.
1965	Chairman, National Research Council, Second Human Kidney Transplant Conference, Washington, DC
1967-71	Member, National Institute of Health Immunobiological Study Section
1970	National Transplant Information Center, Chairman

EDITORIAL BOARDS AND EDITORSHIPS

Transplantation Journal

Journal of Plastic and Reconstructive Surgery

CONSULTANT AFFILIATIONS

1951-56	Courtesy Staff Member, Newton-Wellesley Hospital
1951-	Attending in Plastic Surgery, West Roxbury Veterans Administration Hospital
1952-	Attending in Plastic Surgery, Boston Veterans Administration Hospital
1953-	Consultant in Plastic Surgery, Commonwealth of Massachusetts Crippled Children's Program
1961	Senior Associate in Plastic Surgery, Peter Bent Brigham Hospital
1964-	Chief Plastic Surgeon, Peter Bent Brigham Hospital
1965-68	Surgeon, Associate Staff, New England Deaconess Hospital
1969-	Staff Plastic Surgeon, New England Deaconess Hospital
1957-70	Active Staff, Newton-Wellesley Hospital
1971-	Consultant in Surgery, Newton-Wellesley Hospital
1972-	Consulting Plastic Surgeon, Boston Veterans Administration Hospital

1974-	Consultant in Plastic Surgery, St. Elizabeth's Hospital
1975-	Consultant in Plastic (General Surgery), Massachusetts General Hospital
1976-	Member Oncology Committee, Sidney Farber Cancer Center
1976-	Member Oncology Committee, Children's Hospital Medical Center
1975-	Consulting Medical Staff Plastic Surgeon, Boston Hospital for Women

PUBLICATIONS

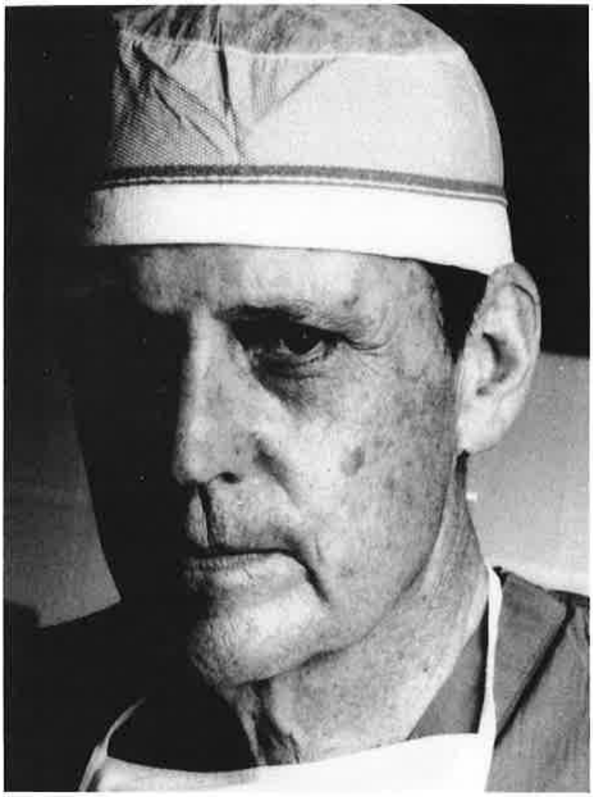
Total: 297

MY THIRTY-FIVE YEAR VIEW OF ORGAN TRANSPLANTATION

Thomas E. Starzl

Address: Department of Surgery
Falk Clinic
University of Pittsburgh School of Medicine
3601 Fifth Avenue
Pittsburgh, Pennsylvania 15213

Thomas E. Starzl



MY THIRTY-FIVE YEAR VIEW OF ORGAN TRANSPLANTATION

Thomas E. Starzl

In my earlier historical reassessments (1-3) and those of Calne (4,5), Murray (6), Moore (7), and Groth (8), the dawn of transplantation was defined as the turn of this century, in part because these reviews emphasized kidney transplantation. Kahan has exposed the incompleteness of this perspective by tracing the roots of transplantation into antiquity (9). Notwithstanding the early traces, evolution of the modern field is a phenomenon of the last 40 years. During the first part of this time, I picked up the trail of renal transplantation and started a new one with liver replacement. From 1958 onward, liver transplantation played an increasingly prominent role in generic advances that were applicable to all organs.

The first known attempts of kidney transplantation in humans were made in France and Germany between 1906 and 1923 using pig, sheep, goat, and monkeys or apes for donors (10-12, translation for 11,12 provided in 10). The first human-to-human kidney transplantation was reported in 1936 by the Russian, Yu Yu Voronoy (13, translation provided in 10). The technique of renal transplantation which became today's standard was developed independently by three different French surgeons, Charles Dubost (14), Rene Kuss (15),and Marceau Servelle (16) and reported in 1951. A number of the kidneys were taken from criminals shortly after their execution by guillotine. John Merrill, the Boston nephrologist had seen the French operation while travelling in Europe in the early 1950s as was later mentioned by the surgeon, David Hume (17), in his description of the beginning (in 1951) of the Peter Bent Brigham kidney transplant program. It was adapted later for the historically important identical and fraternal twin cases in Boston. Although immunosuppression was not available, patients of R.H. Lawler of Chicago (18) and Hume and Merrill (17) may have derived some benefit. In Hume's patient, the kidney graft which was placed in the thigh produced urine for five months.

PHASE I (1955 to 1958)

Although oblivious to transplantation during most of this time, I began experiments in hepatic physiology which led directly to the first efforts in 1958 to replace the liver in dogs. These were stimulated by a clinical observation while I was an assistant resident in training at the Johns Hopkins Hospital in Baltimore (1952 to 1956). In 1955, I helped Dr. Alfred Blalock (Chairman of Surgery) perform a splenorenal shunt on a mildly diabetic rum manufacturer from Jamaica whose diagnosis was cirrhosis of the liver. Afterwards, the patient no longer needed insulin to control his blood sugar.

I wondered if this was because the patient's natural insulin coming from his pancreas into the portal vein had been bypassed around the liver and was therefore made either more effective or more available. The idea became irresistible when I. Arthur Mirsky, a biochemist from the University of Pittsburgh, suggested at about the same time that insulin action was regulated by a hypothetical liver enzyme which he called insulinase. Mirsky speculated that diabetes was a disorder caused by too much insulinase and the consequent need for insulin overproduction.

The idea was tested by animal experimentation at the University of Miami where I finished my general surgical residency in 1956 to 1958. Because there was no large animal facility at this new medical school, I set one up with homemade metabolic cages in an empty garage across from the Emergency Room of the Jackson Memorial Hospital. We obtained dogs from the city pound, made them diabetic with alloxan, calibrated their insulin requirements after they became diabetic, and eventually performed portacaval shunt. To my dismay, the insulin requirements after operation increased drastically instead of diminishing as I had hoped (19). In addition, the animals quickly developed the previously well-known syndrome of "meat intoxication." Now, I became convinced that a different metabolic relationship than I had envisioned must exist between the pancreas (by virtue of its insulin) and the liver. In further experiments, various kinds of blood were used for portal venous inflow. Everything we tried then (19) and for a long time later (20-22) failed to unmask the kind of insulin-liver relationship which I was looking for.

The questions about sugar and insulin metabolism raised by these still primitive thoughts and investigations would require better models, including one of total hepatectomy in large animals. While still in Miami, I developed an improved method of total canine hepatectomy (23) which soon replaced previously used techniques in other laboratories. A fringe benefit was my realization that a new liver for the pursuit of metabolic studies could be installed (I thought easily) in the empty space from which the normal liver had been taken. Work on this possibility was begun in earnest after I relocated in Chicago in June 1958.

While I wasted time in Miami during 1956 to 1958 doing physiologic experiments, efforts in transplantation were going on elsewhere. There was no way of preventing rejection and without such treatment, clinical transplantation could succeed only between monozygotic twins. This step was taken two days before Christmas 1954, with a kidney transplantation from an identical twin donor by Murray et al (24). It was the first example of successful transplantation of a vital whole organ and had a major impact on the field as described elsewhere (2). However, further progress in all other situations would require immunosuppression.

Peter Medawar's appreciation that rejection was an immunologic phenomenon (25,26) made inevitable the efforts to alter the immune system to prevent this process. As early as 1951, Rupert Billingham, working with Medawar and Peter Krohn, showed that corticosteroids delayed skin graft rejection in animals (27,28). Then, W.J. Dempster of Hammersmith Hospital, London, showed that steroids ameliorated established acute rejection after kidney transplantation in dogs (29), presaging the clinical response to this kind of "rescue" therapy that later would soon be seen in many thousands of patients. Dempster also was the first to show the immunosuppressive effects of total body irradiation (30).

PHASE II (1958 to 1961)

The ostensible purpose of returning to Northwestern Medical School (where I had graduated in 1952) was to become fully qualified to do thoracic surgery. This was going to be another passing fancy. I had already foregone a promising career in neurophysiology in which I had obtained a Ph.D., only to abandon this field and to work for a year and a half in heart physiology preparatory to work in cardiac surgery. Now, I was training to be a thoracic surgeon, after having already lost interest in this field. Because the thoracic surgery load was light, I immediately resumed the canine hepatectomy experiments and during July 1958, the first liver transplantations were performed at the VA Research Hospital. This was a project to which I paid more and more attention as time went by after hearing from John Lewis, my thoracic surgery chief at Northwestern, that Norm Shumway, Lewis' previous cardiac surgery fellow at the University of Minnesota, had begun attempts to replace the dog heart at that institution.

A four-page application was sent to the National Institutes of Health and resulted in funds of about $30,000 a year for five years. An unexpected further boost came during the summer of 1958 when Dr. John A.D. Cooper, Associate Dean of Northwestern Medical School, asked me if I wanted to be the school's candidate for a Markle Scholarship. It was an unusual honor because there could be only one nominee from each of the 100 or so medical schools in North America. From the pool of nominees, 20 to 25 would be chosen. Those selected committed themselves to academic careers as opposed to private practice.

The criteria by which the candidates were chosen was not obvious. Fortunately, the judges who were not scientists were insufficiently informed to know how bizarre my proposed career plan was. It is amusing to recall that the committee at the Markle interviews from February 2 to 5, 1959, saw no reason at all why my proposal of liver transplantation could not be accomplished. I was given the Markle scholarship and a few months later began a junior faculty appointment.

Free from patient responsibilities for the first time in four and one-half years, I started on July 1, 1959 to work in the laboratory full time. With grant money in hand, the liver transplant project was transferred from the VA laboratory to the University surgery laboratories in the Montgomery Ward Building at 303 Chicago Avenue. Two senior medical students named Bob Lazarus and Bob Johnson and a third year surgical resident named Harry A. Kaupp Jr., joined the team. Within a few weeks, liver transplantation, which I had been doing alone for the preceding year, including anesthesia management, was perfected enough to have the dogs live through the operation on a regular basis. The secrets were simple.

First, the liver was preserved by core cooling with cold saline or lactated Ringer's solution which was infused into the portal vein at the same time as the liver blood supply was interrupted in much the same way as practiced clinically today except for the solution (31). The second key requirement was a veno venous bypass sytem during the anhepatic period when the native liver was being removed and the vessels of the new organ were being anastomosed to those of the recipient. Otherwise, the consequence of simultaneously obstructing both the portal vein and inferior vena cava for the necessary 30 to 60 minutes was irreversible injury to the intestines and other splanchnic viscera. With the use of plastic bypass tubes which effectively decompressed the obstructed venous beds, the main blood vessels supplying and leaving the liver could be anastomosed with less urgency. The vascular anastomoses were sophisticated ones but well within the grasp of trained surgeons. Biliary reconstruction also was a conventional procedure.

Thereafter, liver transplantation could be done with a reasonable expectation of short-term survival until rejection occurred. By the end of the summer of 1959, we were confident that this operation was not only feasible, but could someday be applied for the treatment of human disease. We had heard by now that a similar project, which also was begun in the summer of 1958, was underway at the Peter Bent Brigham Hospital under the direction of Francis D. Moore.

Our work on canine liver transplantation and that by Moore's Boston team was not generally known until the annual meeting of the American Surgical Association (ASA), held at White Sulphur Springs, West Virginia on April 5, 1960. A paper on the Boston results was read by Moore and published the following autumn in the *Annals of Surgery* (32). As a guest of the society, I discussed Moore's paper (33), based on our impending publications in *Surgery, Gynecology, and Obstetrics* (31,34), the journal of the American College of Surgeons. Moore had presided over the early trials of kidney transplantation at the Brigham. He expected that what was being learned with the kidney model would be applicable to other organ transplants and vice versa. So did I.

Moore was reporting on 31 liver transplant experiments. Seven of his animals lived for more than four days, with a maximum of 12 days before death from rejection. From these seven animals, he had pieced together a very complete picture of the postoperative course after liver replacement in the untreated dog. In my discussion, I described how in more than 80 experiments we had systematically tested different ways of restoring the transplanted liver's blood supply including the omission in some dogs, and the augmentation in others, of portal venous inflow. This was a reflection of my original interest in interorgan metabolic relationships. Livers which were given a normal portal venous inflow performed better than those which were not. The important practical achievement for the moment was that we had 18 dogs with survival greater than four days, with one animal living for 20 and one-half days.

During this meeting, two friendly young men whose faces I recognized introduced themselves in the lobby of the Greenbrier Hotel. One was Dave Hume, the former Harvard surgeon who had started the Peter Bent Brigham Hospital kidney transplant program but who now was at the Medical College of Virginia. With him was Dick Egdahl, and after a few minutes we were joined by John Mannick, who would soon move to Richmond with Hume. In 1978, Mannick would succeed Moore as Chief of Surgery at the Brigham. Although they expressed interest in my work, I was far more intrigued by theirs.

Just before Moore's presentation, Hume, Egdahl, Charlie Zukoski and three other colleagues had given a paper on kidney transplantation in dogs which had been conditioned with total body irradiation (35). The work provided a remarkable insight into the difficulties to be overcome if there ever was to be clinical value of any whole organ transplantation procedure. When Hume's dogs were given more than 1000 rads, rejection of the kidneys could be prevented, but they all died of overwhelming infection. With smaller doses, the grafts were rejected. There was no margin of safety.

It seemed to me that Hume's paper (which Moore discussed) had the same negative implication for clinical use. Hume agreed and told me that he and two of his coworkers (Charlie Zukoski and H. M. Lee) were experimenting with a new drug called 6-mercaptopurine as a substitute for x-ray therapy. Six weeks earlier they had sent an abstract with encouraging results to the Surgical Forum committee of the American College of Surgeons, to be considered for the annual meeting in San Francisco the following October.

This was the first of many personal or phone conversations with Hume, of which the last was at the American Surgical Association meeting at the Century Plaza Hotel, Los Angeles, in April 1973, a few weeks before he was killed in an airplane crash. He always reminded me of a human buzz saw, constantly advancing but with such precision and beauty of motion that it was a masochistic thrill to realize that the cutting pathway was directed straight to you. Few people passed through the veneer and were allowed to see behind. A very friendly and generous man was hiding there.

Both Zukoski's abstract and one of mine were accepted for presentation at the

1960 fall meeting of the American College of Surgeons to which Hume had referred. I had gone beyond simple liver transplantation in that other organs were being transplanted with the liver in what was called multivisceral transplantation (36). Instead of facing its new recipient environment alone, the liver was accompanied by the donor stomach, intestines, and pancreas. Since these were the organs which drained into the portal vein, the transplanted liver could bring with it its own supply of insulin, food, and the other substances which a few years hence would be called hepatotrophic factors.

Only five animals survived the difficult operation, but in each one rejection of the individual organs was less than would be expected if they had been transplanted by themselves. Because the large grafts contained lymph nodes, spleen, and other elements which are part of the normal immune system, it was not surprising to find cells throughout the recipient's own tissues which were thought (but not proved) to have migrated from the graft, reflecting graft-versus-host disease (GvHD) (37). It would be another 13 years before the extent of GvHD, even with transplantation of the intestine alone, would be worked out in rats by the Massachusetts General Hospital surgeons, G.J. Monchik and Paul Russell (38).

My enthusiasm about the multivisceral transplant project was put into the deep freeze by the discussion that followed my talk. William Longmire of UCLA deflated any illusions I might have had about its importance. He asked wryly if it might be easier than performing this complex operation to simply anesthetize the dog and have a laboratory assistant carry the animal from one table to another. The ripple of laughter from the audience completed the humiliation.

Longmire was implying what I already knew, that any such research, including that involving liver transplantation alone, was a technical exercise unless a means could be found of controlling rejection. Stimulated by Hume's report earlier in the year (35), I had already tried to depress the immune system with x-ray therapy before liver transplantation. Irradiation of liver grafts had no beneficial effect and irradiation of the recipient was overtly harmful (39).

The faint hope that remained was the 6-mercaptopurine Hume had mentioned to me earlier and which Calne had described the previous February in two dogs which had survived for 20 and 47 days after similar kidney transplant operations (40). At another Surgical Forum session on the same day as my presentation, Zukoski reviewed the evidence from Hume's Richmond team that kidney graft rejection was weakened and delayed by this drug (41). His results, along with those from earlier skin graft experiments in rats (42,43), and the independent observations by Calne provided hope where there had been none before.

The hope was dim because only a small minority of animals could be kept alive for as long as one month, and none of the kidney recipients had truly long survival. In principle, the dilemma was not different than with x-ray therapy, although the possibility remained that there was a better therapeutic margin. It was also obvious that liver transplantation was much too complicated an operation to use for studies of immunosuppression. The road to the liver would have to lead through the kidney.

Knowing that Joe Murray's Brigham research team was screening immunosuppressive drugs in Frannie Moore's surgical laboratory (Calne would be coming there in 1961), I approached Moore as we walked down the street after one of the forum sessions. I asked him if he would accept me for a research sabbatical in Boston, effective immediately if possible. The fact that I was a Markle scholar gave me a small financial hedge since these funds ($6,000/year for five years) could be transferred between universities. I had not discussed the matter with anyone for the simple reason that leaving Northwestern had not occurred to me until that day.

I can remember how firm Moore was, but also how kind, as he denied my request. I became (and still am) indebted to Moore for his decision which, because it was negative, moved me on to an entirely new level of development and responsibility. Fourteen months later, I left Chicago to be an Associate Professor of Surgery at Colorado. On March 27, 1962, less than three months after arriving in Denver, I performed our first human kidney transplantation on a patient who is still alive 29 years later. Eleven months after that on March 1, 1963, came the first attempt at human liver replacement. As I had concluded in San Francisco, the road to the liver would lead through the kidney, but I would have to find a pathway myself by becoming involved in the renal field.

Deciding to leave Chicago in the space of one day in San Francisco was easier than actually doing it. I had no place to go nor any prospects because I had not been planning to move. However, it seemed to me that the next step in transplantation would not be possible where I was. After a year of exclusively experimental work, I had begun to see private patients in the summer of 1960. The practice grew uncontrollably but almost all of it was being done in private hospitals rather than the Northwestern University hospitals. Overnight, I had become a commercial surgeon and by so doing had freed myself from debt for the first time in more than 10 years. But the time and energy to accomplish this had been stolen from the research program which was the justification for my Markle scholarship.

A way out was found for me by Ben Eiseman, who was Chairman of the Department of Surgery at the University of Kentucky. William R. Waddell, the newly appointed Chairman of Surgery at the University of Colorado, was looking for someone to fill the position of Chief of Surgery at the Denver VA Hospital, an appointment held by Eiseman until his departure for Kentucky. This was one of the best nonchairman jobs in the United States. Eiseman recommended me to Waddell who subsequently came to Chicago in the summer of 1961 to discuss the possibility. Waddell wanted transplantation to be an imprint of his new department. Although he had no experience in the field, his long stay in Boston had exposed him to the much publicized activities at the Brigham. His own affiliation at Harvard always had been at the Massachusetts General Hospital, but he was friendly with Dave Hume, Joe Murray, and Frannie Moore.

We agreed on the goal of bringing liver transplantation to clinical use. However, we also realized that it could not be attempted until kidney transplantation, an operation which had almost universally failed until that time, could be made to work. I told him that no single agent or drug, would allow us to accomplish anything more than had been done by the pioneers whose efforts in the kidney field are described in other contributions to this volume.

To avoid a false start, we would follow the tracks of Joe Murray and John Merrill (24) by beginning with an identical twin case in which immunosuppressive treatment was not necessary. Waddell, whose move to Denver in July 1961 preceded mine by almost six months, knew of a 27-year-old patient who had a potential identical twin donor. The potential recipient was being cared for at a Denver private clinic. The attending physician had promised to hold his patient for transplantation until my arrival, instead of sending him to Boston as he originally planned.

Waddell and I placed a high priority on duplication of the Northwestern transplant laboratory at the VA animal facility which was essentially unused by surgeons following the mass exodus of Colorado faculty during the preceding year. The laboratory had been cannibalized by other departments, and nothing was left for us except for a small operating room with a kennel across the hall that could accommodate 30 or 40 dogs.

What we aspired to seemed like lunacy to some of the people whom we recruited to the transplant team from the existing faculty in January 1962. In spite of these doubts, the identical twin transplantation went forward in March 1962. Both the donor and recipient teams had practiced the operation many times on cadavers in the morgue, and by the time of its performance there was little reason for anxiety. The result was perfect (44). Both the patient and his donor remain well more than 29 years later.

PHASE III (1962 to 1963)

At the time of our identical twin transplantation, artificial kidney machines had appeared in the United States but were used primarily to tide patients over during an acute but reversible bout of renal failure (7). Transverse incisions to insert the plastic tubes into the patient's vessels for connection to the machine would start at the wrists, moving upward every few inches to find new access sites until the axillae were reached. Each site was used three or four times. When the arms were used up, the incisions would start at the feet and move up to the groins. Once the leg vessels were exhausted, the string had played out.

This was changing after the introduction in 1960 of the Schribner shunt for chronic dialysis at the University of Washington. However, blood vessel access was not the only problem. In 1962, very few artificial kidneys were available. The problem was dramatically publicized in *Life* magazine, November 9, 1962, by pictures of a tribunal in Seattle deliberating on which six patients among many candidates should be selected for entry into the only artificial kidney unit in the world equipped for chronic care (45).

Dr. Joe Holmes, the Chief of Nephrology at the University of Colorado, had the equipment, skill, and experience to use the new technology. Approaching 60 years, he became the oldest member of the transplantation team. Chronically fatigued by overwork and lung disease which he aggravated by constantly smoking cigarettes, he fought to treat or hold back the tide of desperate patients who flocked to Colorado General Hospital after the publicity of our identical twin transplantation.

One of these patients with renal failure was a 12-year-old Black boy named Royal Jones. His arrival was too early, because we were not ready to treat him and would not be for another half year. Holmes agreed to try to hold Royal Jones on dialysis and the countdown began. The VA transplantation laboratory for which we had been slowly acquiring equipment and personnel sprang into action. It was possible within a few weeks to perform eight or 10 dog kidney transplantations in a day or twice this number if necessary. A supply of the 6-mercaptopurine or its derivative BW 57-322 (Imuran), which was receiving its first trials at the Brigham, was obtained from George Hitchings of the Burroughs Wellcome drug company.

We were particularly interested to see if x-ray therapy could be combined with Imuran since the only genuinely promising results of which we had knowledge in other than twin cases were those of the French teams of Rene Kuss (46) and Jean Hamburger (47). They had used irradiation. However, in our dogs given total body irradiation at the same levels planned for Royal Jones a disquieting effect was seen. Many of the canine kidneys quickly became enormously swollen and cyanotic, seemingly worse than in untreated animals. Only an occasional animal had prolonged survival.

The results were the same as Hume had reported in dogs (35). Our pessimism was reinforced by the discouraging results in the clinical irradiation trials at the Brigham (48,49).

The best results were with Imuran. Some of these dog recipients lived on for years, long after discontinuance of therapy. It was demonstrated unequivocally that prednisone therapy could reverse rejection but caused death from its own side effects of which ulceration and bleeding from the intestinal tract were almost invariable (50). These observations were not published until long after the clinical steroid trials were underway (51). Our conclusion by the autumn of 1962 was that survival for 100 days or more with any single agent could be achieved in only one of every four or five mongrel dogs. There had been no time to test all of the treatment combinations.

What to do with this incomplete information, and with similar observations reported by Calne and Murray from the Brigham laboratories at the Surgical Forum in October 1961 (52), was our quandary. Adequate hemodialysis for Royal Jones was becoming more difficult daily because of exhaustion of his access sites. The transplantation with a kidney from his mother went forward on November 24, 1962, with combination treatment by irradiation, Imuran, and prednisone.

To protect him from infection, he was kept in one of the Colorado General Hospital operating rooms for a month afterwards during which he had a moderately severe rejection which was reversed easily with large doses of prednisone. A few weeks following this, he returned to school. The transplant lasted until 1968, and then was replaced with a second graft. Many years later, the second graft also failed. Royal is still alive awaiting his third kidney nearly 29 years later.

The success could have been a fluke. During the next 12 weeks, three more kidney transplantations were performed but omitting total body irradiation. Two of these patients who were treated with Imuran and prednisone also are alive, both with their original grafts from a brother or sister. The third patient named Bill Sinclair died of infection 113 days postoperatively. After the transplantation, a large thrombus in one of his leg veins migrated to his pulmonary artery from where the embolus was removed at an emergency operation by Dr. Tom Marchioro, now Professor of Surgery at the University of Washington. Sinclair never fully recovered but his new kidney, which had been donated by his wife, functioned well until the end. It seemed to us that the immune barrier now had been surmounted repeatedly. The stage was set for liver transplantation. It never would be this easy again, in part because our strategy in the kidney program had emphasized the use of related donors and in part because liver transplantation was a vastly more difficult operation.

The first attempted liver transplantation on March 1, 1963, ended in tragedy. The patient was a 3-year-old child with biliary atresia which had brought him to the miserable last days of his life in a condition which today might be considered beyond help by transplantation. The donor was another child who died during an open heart operation. In looking back, one can ask why the liver recipient, who himself was on life support with a ventilator, should not have donated a heart to the other child instead of receiving his liver.

The question did not come up because the first heart transplantation in Capetown was four years in the future. Instead, the donor who already was on a heart-lung machine was cooled while the artificial circulation was maintained. Although we had performed nearly 200 liver transplantations in dogs, nothing could have prepared us for the difficulties in the recipient which were caused by portal hypertension, scarring from previous operations, and a complete lack of clotting. The patient bled to death.

During April and May 1963, more kidney transplantations were performed. Of the first six nontwin recipients, four were destined to survive for the next quarter century. By now, research in the laboratories turned back to the more difficult operation of liver transplantation. The main lesson that had been learned from the first liver case was that the defective blood clotting found with terminal liver disease would have to be controlled. A German coagulation expert named Kurt von Kaulla who was working in the Department of Surgery was recruited to the team. Von Kaulla recommended strategies to shore up defective clotting factors with infusions of purified blood products and to control fibrinolysis with epsilon amino caproic acid (EACA).

In 1962 and early 1963, the University of Colorado did not have the high visibility in the national media which it later enjoyed, or labored under. Only when Bill Waddell announced it while discussing a paper given by Hume in April 1963 at the American Surgical Association in Phoenix, Arizona did the existence of the Colorado kidney program become generally known (53). Before then, Waddell was in contact with Joe Murray and his other friends at the Brigham in Boston. Dave Hume called me almost daily from Richmond for information about the course of our patients. Both Murray and Hume seemed interested only in the kidney cases. The failed first attempt at liver transplantation went unnoticed by the press.

At the 1963 American Surgical Association meeting, I met Will Goodwin, one of the world's foremost urologists and a pioneer in transplantation in his own right. Several years earlier, Goodwin had attempted several kidney transplantations at UCLA. From these cases, a number of important observations were made which would be of great help to later workers. The death of all his recipients had discouraged him and caused him to stop clinical trials.

In one of Goodwin's patients, he had seen reversal of kidney rejection by steroids in a woman who also was treated with the anticancer drug, cyclophosphamide (54). She survived for 160 days and was the first example of long survival of a human who was treated with drugs only, using a drug combination that was extensively evaluted a decade later (55). Goodwin's historic kidney transplantation was in September 1960. However, the observation of steroid responsiveness was not published until 1963 and was unknown to me. After talking to Goodwin in Phoenix, I added a discussion of Goodwin's case to our paper but failed to annotate the basic literature on steroid immunosuppression (27-29) and the clinical observations on steroid therapy previously made by Kuss (46) and Hamburger (47). This was unintentional neglect.

Beginning in 1962, we had been using Imuran plus prednisone, and our conviction was that prednisone was the dose maneuverable component of this first version of modern day immunosuppression. The Imuran-steroid combination was the secret of our unexpected success and in our manuscript containing this message (51), we emphasized two other points: the reversibility of kidney rejection with high dose steroid (prednisone) treatment, and the "tolerance" which allowed lightening of maintenance immunosuppression in the weeks and months after a successful kidney transplantation.

While we talked in Phoenix, Goodwin told me of an impending meeting on renal transplantation in Washington, DC, scheduled for September at the National Research Council. He said that he would arrange invitations for me and for Bill Waddell. A few days later, Goodwin came to Colorado. I learned later that his habit was to glean information from these informal visits and to report it in memoranda to the UCLA transplant group which included Paul Terasaki. More than 27 years later, in November 1990, a urologist named Jacques Poisson of Nice, France gave me a yellowed copy of a six-page single-spaced intramural letter from Goodwin which Poisson had saved from his fellowship days with Goodwin in Los Angeles. Dated May 11, 1963, the in-house document started:

"Dear Friends: On May 5 and 6, I visited Denver to learn what I could of the homotransplantation effort of the group there (Tom Starzl, William Waddell, Tom Marchioro, Oliver Stonington, and about a dozen others). The visit was most impressive to me, and I should like to share some of my impressions with you.

When I arrived on the evening of May 5, I went to the Veterans Hospital where I visited the completion of what must surely be the world's first technically successful homotransplantation of the human liver. The recipient, a patient of Dr. Waddell's, was a man with a primary hepatoma involving the whole liver. He had had two explorations, 7 days and 1 day before the transplant. He was a non-veteran admitted to the VA Hospital in order to receive the transplant from a VA patient dying there of a brain tumor. The surgical team was waiting alerted for 48 hours, one of the drawbacks of cadaver donor transplantation.

When the white donor (the recipient was Afro-American) finally died, Dr. Marchioro and his team promptly introduced a catheter via the femoral vessel and began perfusion (up into the aorta) at a slow rate with a heart-lung machine that was primed with refrigerated oxygenated glucose solution plus procaine. Later they opened the chest and also perfused the lower aorta and abdominal organs from above.

Preparation of the sterile donor liver took about 2 hours. Approximately, another 2 hours were spent in transplanting the liver, performing all the necessary anastomoses. When I saw the homotransplant in place, it had a good color and looked like a normal liver. A cholecystectomy was done and the gall bladder bed bled in a healthy normal way. A T-tube was placed in the common duct below the anastomosis and shortly thereafter, it began to drain clear bile. The above surgical procedures were done . . . with great skill and careful speed. . . . They had tried this some weeks or months ago in a child with congenital atresia of the bile ducts. The procedure failed because the recipient bled to death under their eyes. There was lack of blood clotting. Because of this awesome previous education, they were prepared in the present case, and gave large amounts of human fibrinogen intravenously during the operation.

The next day, I saw and talked with the patient. His new liver was making large amounts of clear bile and he seemed to be in good immediate postoperative condition. It seemed to me that the patient was in better shape than the surgeons on the day after this monumental effort."

The rest of Goodwin's letter was concerned with the kidney recipients, many of whom he interviewed. As it turned out, the patients to whom he talked are still alive. Goodwin went on:

"The Denver team has either 8 or 9 successful kidney transplants (2 or 3 since dead) . . . Another patient I was privileged to see is a 35 year old male who had come from Virginia to the Denver VA because he was told that the Denver and Los Angeles VA Hospitals were "centers" for kidney transplantation. Denver was closer than Los Angeles, but somehow he got past Richmond and Hume. He received a kidney from his 32 year old sister in January, 1963. Before that, he had dialysis in Virginia (at the VA Hospital), and in Denver in preparation for the transplant. He appeared to be in excellent health. He had a moon face and ruddy cheeks. He confessed to an interest in sex and erections but evaded the question of whether or not he had intercourse (he is a bachelor). He apparently is presently a ward of the VA, and is being rehabilitated. I think that he takes Imuran and prednisone and I believe that he formerly had chronic glomerulonephritis. He was a truck driver."

This patient also is still living with his graft which is the longest surviving nontwin kidney transplant in the world. It is interesting that there was an ABO blood group mismatch. He was B blood type and his sister donor was A.

A cadaver organ procurement program was a necessary condition for the Denver program and particularly interested Goodwin. Brain death and the concept of the heart-beating cadaver were five years away. Consequently, all donors were without a heart beat and circulation for five to 30 minutes before an artificial circulation could be restored with a heart-lung machine (56,57). Goodwin had not heard of this method and wrote:

"Tom Marchioro has worked out and is the driving force behind an active and intelligent program to harvest cadaveric organs (especially kidneys) for homotransplantation. . . A very low pressure system is used with low rates of perfusion (aortic) so that the blood inflow (to the pump) matches the output. They feel that this is valuable and useful and have had some good animal experimental data to support them. . . A visit to their dog lab at the VA Hospital was most impressive. It is a well run, active place, air conditioned, and clean. They have plenty of technical help. They keep superb records on their animals, similar to regular hospital charts. They have one doctor in full time charge of records alone. They have a number of excellent kidney transplant experiments going on to test the value if any of splenectomy, thymectomy, etc. They also have an active program with liver transplants."

Goodwin's six-page single-typed memorandum is too lengthy to reproduce in its entirety, but near its end was a comment about the interactions within any multidisciplinary group, showing Goodwin's grasp of human behavior:

"One of the interesting human aspects of this work, not only in Denver but everywhere, is how much each participant wants to be a part of the team and how each of us speaks so readily of "our experience," while privately considering it "my experience." Everyone with whom I speak is eager and ready to give credit where due, and at the same time wants to ensure his own niche and his own credit."

Reading his report nearly 28 years later, I wondered if Goodwin might have set new standards in journalism had he not committed himself to surgery. He saw everything that was significant. The clotting problem had been dealt with in the liver recipient whom he observed, and the kind of management during operation which he described became standardized over the years. However, the strategy of coagulation control had a delayed backfire in this case and in the next three liver transplant recipients who followed. During the time when the livers were sewed in, the plastic external bypasses were used to reroute venous blood around the area of the liver in the same way as had been worked out in dogs.

In the humans who were being given drugs and blood products to promote clots, these clots formed in the bypass tubing and passed on to the lungs. There, they caused abscesses and other lung damage which contributed to or was the cause of delayed death of not only the patient seen by Goodwin (who died 22 days later) but in three more recipients who had otherwise successful liver transplants in June, July, and October 1963 (57,58). A pall settled over the liver program, and no more patients were entered for more than three years. It was the beginning of a self-imposed moratorium. By this time, single patient trials had failed at the Brigham (59) and in France (60).

When Goodwin left Denver in early May 1963, he realized the regularity with which rejection could be controlled in kidney recipients using the Imuran-prednisone treatment. However, in his lectures, he always warned "Don't promise more than you can deliver," and illustrated the point with the photograph of an ancient statue of one of the Greek gods who was sparsely clad. Wrapped around the god's leg was a voluptuous maiden, expressing some unfulfilled desire, the nature of which was left to the amused audience's imagination.

Throughout the spring and summer of 1963, our pace of kidney transplantation increased, and the series had reached 30 by the time of the Washington kidney transplant meeting in September 1963. This conference to which Waddell and I were belatedly invited was a small one, with only about 25 contributors. However, almost all of the key workers were there who had brought the field this far. Here, I first met Joe Murray, John Merrill, and other members of the distinguished Brigham group. The French and English pioneers also were there including Ralph Shackman, Ken Porter, and Roy Calne. I was uneasy and felt like someone who had parachuted unannounced from another planet onto turf that was already occupied.

By this time, I had started writing a book, *Experience in Renal Transplantation* (61), which was to be published the following summer. In its introduction which already was in the hands of the printer, I already had summarized the work of these men. After describing the dismal record to date, it went on:

"... *Despite these encouraging findings, it was not yet possible to obtain consistent success with homotransplantation procedures, either in experimental animals or man. Like the elusive jigsaw puzzle, in which many of the pieces had been fitted into their appropriate slots, the picture was not yet complete. The pioneer efforts of Murray, Kuss, Hamburger, and Hume had all demonstrated that a renal homotransplant was capable of protracted function in the occasional case. If this could be achieved sporadically, it seemed reasonable to expect that the proper manipulation of a number of small details might provide a consistently successful solution. Despite this expectation, almost all renal homotransplants had failed when, in the spring of 1963, Goodwin and Martin compiled the known renal transplants from various centers throughout the world. Less than 10 per cent of those cases treated to that time had survived for as long as three months. The courageous and often tragically unsuccessful attempts of the early pioneers provided a vast, although frequently uncatalogued, background of valuable information upon which future progress might be built* . . . "

These were the kidney transplant pioneers. What we had done was to complete their story. At the same time, we realized for the first time in Washington that we had more surviving kidney transplant recipients than everyone else combined. Determining the eventual outcome of these patients would be important. This was made possible by the creation at the conference of a worldwide kidney transplant registry, which would be based in Boston. The impetus for this extraordinary compilation came from Joe Murray.

The meticulousness of the registry report (62) made it possible 25 and one-half years later in the summer of 1989 to trace the fate of all 342 nontwin kidney recipients who had undergone transplantation throughout the world from the beginning up to the end of March 1964 (63). There were 24 25-year survivors, of whom 15 were from our original Colorado series. The nine others were still alive at six other centers. These included three of Dave Hume's original patients at the Medical College of Virginia, two from the University of Minnesota (Kelly and Lillehei), and one each from Boston (Murray), Cleveland (Kolff), Edinburgh (Woodruff), and Paris (Hamburger).

In this look-back, none of the world's 24 quarter-century survivors had been given an unrelated donor kidney. Nor was there an example in the world of a 25-year survival of a cadaver kidney allograft (63). One of Hamburger's cadaver kidney recipients in Paris finally passed this barrier on October 12, 1989. This was not surprising. Inferior results with unrelated donors were evident even at the time of the Washington meeting.

Because liver and heart grafts could be obtained only from cadaver donors, what had been learned so far was not an invitation to go forward with the extrarenal trials. Better antirejection treatment than the Imuran-prednisone combination must be developed or else a means had to be found to better match up the donors to the immune system of the recipient (tissue matching). Apart from the deaths that already had occurred, this was the main reason why the liver program was closed for three more years. Our primary mission of liver transplantation had failed. Instead of introducing a new treatment for liver disease, we had succeeded only in making kidney transplantation practical. Not long after, Waddell remarked that we had climbed onto the wrong tiger and would find it hard to get off. I soon understood how right he was.

After the Washington meeting, several of the conference members came to Denver for a first hand look: Hume, Porter, Shackman, Kuss, and Kuss' young associate, Jacques Poisson. While there, Porter agreed to write the section on kidney transplant pathology for my impending book on renal transplantation. His chapter was a classic which was years ahead of the field. Before long, his interest turned to liver transplantation and stayed there for the next 28 years.

Elsewhere, the kidney gold rush began. At the beginning of 1963, the only active kidney transplant programs in the United States were at the Brigham, in Richmond, and at the University of Colorado. More than 25 new ones sprang up in the United States alone within the next year. We were inundated with fellowship applications, providing a talent pool from which came many of the leading figures in transplantation of the next generation. Kidney transplantation seemed to have become a clinical service overnight.

This was partly an illusion. It would not be possible for many more years to safely transplant cadaveric organs of any kind, including the kidney. Well into the late 1970's, Terasaki reported a compilation from 105 American programs of nearly 5,000 cadaveric kidney cases in which the one-year graft survival was only 45 percent with an average patient mortality of nearly 20 percent (64). Individual centers tended not to report their own poor results, erroneously believing that everyone else must be doing better.

During the peak of the professional euphoria, many major hospitals had acquired artificial kidney capability, with the result that patients who would have died only one or two years earlier could be kept in reasonable condition while they waited for a transplant. Serving their needs was almost entirely dependent on live donors because brain death as a condition for cadaveric donation was five years in the future. Desperate potential recipients were piling up faster than places could be found for them for dialysis support, a service for which most health insurance agencies refused to pay because it was "experimental."

At the height of the crisis, heterotransplantation was reexplored. On February 16, 1963, Dr. Claude Hitchcock of Hennepin County Hospital, Minneapolis, transplanted the kidney of a baboon to a 65-year-old woman. The organ functioned for four days before its artery clotted (65). The case was not made public until it was learned later in 1963 of a far more encouraging experience by Dr. Keith Reemtsma of Tulane University using the the closer-to-human chimpanzee donor (66). One of Reemtsma's chimpanzee kidney grafts functioned for nine months. Reemtsma also transplanted a Rhesus monkey kidney which was fiercely rejected.

Convinced that his own first failure was due to a defective surgical operation and that the baboon would be an acceptable kidney donor for humans, Hitchcock called me about exploring this possibility for our patients with urgent need. He already had a strong collaboration with the Southwest Primate Foundation, an outstanding primate center in San Antonio, Texas. Baboons were bred there, and their medical records were kept for their life time. Infecting patients with baboon diseases seemed unlikely. An international consortium of primate experts descended on Denver.

Six patients were given the baboon kidneys at Colorado (67). All of the organs functioned promptly and maintained function for 10 to 60 days. However, the necessary doses of Imuran and prednisone were very high, and eventually the grafts were rejected. As judged by Porter, the rejection was midway in severity between that of the chimpanzee and Rhesus kidneys but not qualitatively different than in some homografts in which there was a humoral component. The same events were recapitulated two decades later in the Baby Fae baboon-to-human heart transplantation in spite of much improved immunosuppression (68). It was clear that the use of animal organs would have to wait for better and possibly fundamentally different immunosuppression. The chimpanzee would be excluded from future consideration because of the threat to its extinction and because its anthropomorphic qualities were increasingly recognized (69).

PHASE IV (1964 to 1966)

After the dust settled, a new era began - this one of consolidation, confirmation, and sober reflection about what had been done. Will Goodwin, whose memorandum of May 1963, was quoted in Phase IV, now wrote another one to his UCLA team, reflecting the amazing events in the intervening 11 months. Like the first document, this one was found in Nice, France, in the memorabilia which Jacques Poisson had saved. After a lengthy description of the papers (many on transplantation) given at the 1964 American Surgical Association (April 1-3, Hot Springs, Virginia), Goodwin concluded:

". . .It seems to me that we are now in a kind of "second phase." Many have more confidence than before and are beginning to look for longer range successes. At the same time, we should go slowly to study and observe some of these strange things that are being seen, such as peripheral neuropathies and vascular lesions, etc. I would not be surprised if one of the most interesting things that could come out of all of this will be observations of what may turn out to be "new diseases" in some of these long range survivors."

Goodwin was prophetic. The most obvious derivative diseases were those caused by the steroids which were essential for consistent success: redistribution of body fat with moon facies and the typical "buffalo hump," growth arrest in children, damaged and thinned skin with abdominal stretch marks, cataracts, bone demineralization and joint decay, myopathy, peripheral neuropathy, and secondary diabetes. The quality of the recipients' lives as well as freedom from lethal opportunistic infections were inversely related to the amount of steroid therapy needed to retain function of their new kidneys. It was soon learned that low steroid dose requirements could be expected only if the donor was a family member.

Even under these circumstances, it was tempting to bring to conferences or symposia only those patients who had been recently operated upon, before the stigmata of steroid treatment became visible. A further specter emerged when several of our earliest recipients developed a malignant tumor (then called a reticulum cell sarcoma, later classed as B-cell lymphomas) in the brain, liver, or elsewhere (70). It was soon apparent that these and other cancers would be seen in increased numbers in these patients (71,72). Israel Penn, now Professor of Surgery at the University of Cincinnati, began a worldwide registry of these cancers in transplant recipients; at the end of 1990, more than 5,000 had been entered. The complication was attributed to the loss of immunologic surveillance, but evidence supporting this hypothesis was at first marginal (72). Years later, after the demonstration that the Epstein-Barr virus caused the B-cell lymphomas, it was shown that these lymphomas usually involuted when immunosuppression was stopped (73).

Appreciation that kidney transplantation was a still imperfect new form of treatment was a powerful stimulus to find better ways of immunosuppression, or else to find ways to improve tissue matching and thereby reduce the amount of immunosuppression which was needed. Strategies to achieve both objectives were put in place during a half year moratorium on new kidney cases which was decided on in Colorado, beginning in the spring of 1964. Ripples from these strategies can still be seen almost three decades later.

The first step was a trial of tissue matching. What to measure, and how, were unanswered questions. We already had shown the importance in kidney transplantation of compatibility of the ABO blood group antigens. About half of the ABO incompatible kidneys were rejected within minutes or hours, presumably because of binding of the isoagglutinins to ABO antigens in the cells and blood vessel endothelium of the kidney grafts. From this experience came the rules of ABO compatibility for kidney transplantation (74), which later were shown to apply to the liver, heart, and other solid organs (75).

Beyond ABO matching, it was predicted by many of the Washington conference participants of 1963 that tissue matching would improve the reliability and predictability of rejection control. Felix Rapaport, one of the conference members, already was a star in transplantation because of his work in histocompatibility. Paul Terasaki's name was frequently mentioned in such discussions because he recently had developed his microcytotoxicity technique which he thought detected histocompatibility antigens in the lymphoid cells. The concept was the same as that advanced earlier by Dausset (76) using a different antibody detection system and subsequently supported by collaborative investigations with Rapaport.

Workers in Holland, Italy, Denmark, England, and the United States began to search for other antibodies, believing that by back tracking the antibodies, they might be able to identify the tissue antigens which had evoked them. If this were possible, the practical next objective would be to match up these antigens in donors with the antigens of prospective recipients. This was the beginning of human histocompatibility research, a new field of indescribable importance and complexity which made intelligible many previous mysteries of the human immunologic system and certain aspects of immune rejection of transplants.

By 1963, the list of antibodies which seemingly reacted with different human tissue antigens was long enough to convince Terasaki that matching efforts in future cases might be worthwhile. However, he wanted to begin by studying the antigens in

O to non-O*	Safe
Rh- to Rh+	Safe
Rh+ to Rh-	Relatively safe
A to non-A	Dangerous
B to non-B	Dangerous
AB to non-AB	Dangerous

*O is universal donor, AB is universal recipient [Reproduced from (74)].

patients bearing successfully transplanted kidney grafts, comparing those with the antigens in their donors, and seeing if there was any relation of the fit of the antigens with the clinical outcome. A positive correlation of good matching and good outcome would establish that the antigens being studied second hand through their reaction with the antibodies were the crucial ones involved in rejection. This was Terasaki's hypothesis and that of Dausset and Rapaport.

Knowing from Goodwin's report from the Washington conference that most of the kidney transplant survivors were in Denver, Terasaki came to Colorado after the meeting, rounded up the recipients and their donors, drew blood samples, and estimated the antigen match with his still impure and incompletely classified antibody panel. To everyone's delight, many of the most trouble-free recipients were those whose white cell antigens closely matched those on the donor's white cells. The clue was tenuous because there were so many exceptions and also because most of the successfully transplanted kidneys came from sibling donors or from parents who had donated to their children (77).

The retrospective study was finished by autumn and when our kidney program was reopened in October 1964, it included the first effort ever made at prospective matching (78). At the time, kidney donation in Colorado was still being accepted from volunteer convicts at the Canon State Prison who were numerous enough in many cases to allow a choice amongst as many as 50 or 60. In spite of the size of the unrelated donor pool, it was difficult to find a perfect or even good match whereas very complete matches were encountered frequently if there were multiple potential donors within a family.

The results when the transplantations were actually performed were disappointing. The matching in unrelated cases, although never complete, was better than that previously achieved by chance when no such efforts had been made. However, no difference could be seen in the recovery of patients who received kidneys from these relatively well-matched versus completely mismatched donors or in the histopathology of the grafts which were graded by Porter after biopsy.

The results were reported as "preliminary" in 1966, but by 1969, I was alarmed by the continued lack of correlation between clinical outcome and quality of matching in unrelated cases (by now largely cadaver donors) and concerned about my role in starting these epidemic efforts at matching five years previously and spurring them on subsequently. We collected clinical data on all of our patients in whom we had tissue typing information from the beginning of our Colorado program in 1962 until the present and arranged the first of several grueling work sessions at Terasaki's laboratory. The conclusion was that typing was not a discriminating instrument of donor selection using unrelated donors, that it could be used to select ideal donors within families, and that short of perfect matches, it was only equivocally helpful even within families.

Reports of these results at nephrology and surgery meetings (79) created a furor in the typing fraternity. The evidence was that the antigens being matched were transplant antigens which followed classical genetic (Mendelian) laws (witness the sibling results) but that the system was so complex (more than we were measuring) that matching would not be the boon we had predicted. Terasaki suspected that there might be a "center effect" in which experience and skill with immunosuppression covered up a typing effect or that the sample size was too small to test the original hypothesis.

He set out to collect 1,200 cases from multiple centers. The original conclusions were validated and the new analysis was presented by Terasaki to the Transplantation Society in The Hague on September 8,

1970. Anxious and looking smaller than I remembered him, Paul walked resolutely to the podium and read his message to a huge and it seemed to me hostile audience. When he finished, there was little applause.

Within a few weeks, the federal agency funding Terasaki's UCLA laboratory paid it an emergency site visit and discontinued its support. Terasaki's heretical report was not welcome, and now the messenger must be killed. Before long, others came forward with evidence that Terasaki's conclusions were correct. Terasaki had been right not only about what typing could do, which was considerable for intrafamilial transplantation, but what it could not do in less than perfectly matched cadaveric cases. Twenty years later, the only controversy is whether matching under all other circumstances means enough to be the primary determinant of cadaver kidney distribution. Shorn of his government contract, Terasaki saved his laboratory by other means. Full of honors now, he has remained to haunt the perpetrators of the inequity for the next two decades (80).

By exposing the truth, Terasaki had made it clear that improvement in clinical transplantation would depend primarily on better drugs and other improved treatment strategies, not by vainly hoping that the solution would be through tissue matching. Although it was not appreciated at the time, Terasaki's conclusion breathed life into the still struggling fields of liver and heart transplantation since patients needing these organs did not have recourse to artificial organ support analogous to the artificial kidney while they waited for a well-matched donor. It was a relief to know that the selection of donors with random tissue matching would not result in an intolerable penalty.

Ironically, the supreme practical contribution of tissue typing proved to be the detection of those cytotoxic antibodies which attracted Terasaki's attention in the first place. At the First Histocompatibility Tissue Matching Conference (June 7-8, 1964, in Washington DC), Terasaki described how these antibodies if directed against the cells of the donor can cause hyperacute kidney rejection in the same way as with blood group mismatches (81).

He recommended the cytotoxic crossmatch test which is carried out today before every kidney transplantation anywhere in the world. The credit for this major contribution often is given to someone who was in the 1964 audience and reported the same thing almost two years later. When the details of hyperacute rejection were worked out later, including the similarity of this catastrophe to the Schwartzman reaction (82), Terasaki was a collaborator, and in the late 1970s he defined the kinds of antibodies which were dangerous and which were not.

The tissue matching strategy was played out in the clinics. In contrast, improvement of immunosuppression was a laboratory project from 1963 until the first clinical trials of ALG were begun in 1966. However, the first order of business was an Imuran project with liver transplantation. Our original premise of developing a kidney transplant program as a pathfinder for the technically more difficult liver procedure (83) came into question. When no one was able to obtain truly long survival in dogs, or even survival beyond 30 days after liver replacement, there was growing suspicion that there might be some fundamental difference in rejection of the liver which made this organ more difficult to protect.

After Porter's visit to Colorado in September 1963, 150 canine liver transplantations were performed at the rate of four per week at the Denver VA research laboratories with weekly or twice weekly shipments of the resulting tissues to London. One of the liver recipients from the series (84) lived for almost 12 years before dying of old age. Half of the animals treated with Imuran lived for 25 to 50 days and about one in five survived three months or longer. The results were better than with dog kidney transplantation, using Imuran alone. At a greater frequency than after kidney transplantation, it was possible to stop treatment after three or four months without evidence of subsequent rejection (85).

The possibility was raised for the first time that rejection of the liver might be easier to control than that of other organs (84,85). Subsequently, much stronger evidence that this was true was provided from pig experiments by Garnier (86), Peacock (87), and Calne (88). The pathologic studies by Porter filled in other missing information (89). He redefined the features of acute rejection, delineated those of chronic rejection, and laid the basis for needle biopsy interpretation which became a cornerstone of modern management of liver transplant recipients.

These liver transplant experiments settled the issue of feasibility but not of practicality. For human cases, all livers would have to come from cadaveric donors. These nonrelated organs would be more difficult to protect from rejection than the "easy" intrafamilial human kidney transplantations that had fanned our enthusiasm in 1962 and 1963. The next project was the development of ALG.

Ken Porter was the person who suggested the ALG project. He knew of work in progress on antilymphocyte serum (ALS) in rats by Michael Woodruff and Keith James of Edinburgh and by other workers in Britain. The principles of ALS therapy had been known since the time of Metchnikoff who immunized guinea pigs with rat lymph nodes or spleen cells and then demonstrated that the guinea pig sera lysed rat monocytes (90). With a flash of clairvoyance Metchnikoff suggested the use of such sera to eliminate the cell lines guilty of causing certain human diseases (later shown to be autoimmune). Sixty years later, the pursuit of this fantasy would take a detour through transplantation.

In modern times, ALS preparations to prevent experimental skin graft rejection were first used at Yale University (Byron Waksman) (91), Edinburgh (Michael Woodruff) (92), and at Harvard (Tony Monaco and Paul Russell) (93). A tidal wave of publications followed including those from Medawar's laboratory (94). In these experiments, rabbits were immunized against the lymphocytes of mice, guinea pigs, or rats. The rabbit serum was injected intraperitoneally in the treated animals. Skin grafts placed between mice, between guinea pigs, or between rats survived for prolonged periods.

The infusion or injection of raw animal serum into humans was not a particularly palatable idea, especially when the dosage into the abdomen would be several gallons if the experimental information was applied to clinical practice. In addition, a larger animal than the rabbit would be preferable in which to raise the antibodies against human lymphocytes. The horse was a candidate. Finally, there was no reason to give the whole animal serum to patients when the antibody activity was presumably limited to some small fraction of which the location was suspected but not proved.

By the end of 1965, we were far along in research on ALS but with a different purpose than the purely scientific ones being pursued in most other laboratories. We were gearing up for clinical trials. We had selected the horse as a serum donor, identified the gamma globulin as the target for refinement of the antilymphocytic antibodies in the horse serum, learned how to remove and purify this fraction which we called antilymphoid globulin (ALG), and devised test tube analyses which would allow us to estimate its potency. The leader of this research team was Yogi Iwasaki, a Japanese surgeon who today is Chairman of the Department of Surgery at Tsukuba University near Tokyo (95). When he returned home, he sent another surgeon, Noburu Kashiwagi to take his place (96). Kashiwagi now is Professor of Experimental Surgery at Kitasato University.

Every step in the process and its totality were tested in the dog with both kidney and liver transplantation (97). For these animal experiments, dog ALG was prepared using dog spleen and lymph nodes to immunize the horse. For human ALG, the spleens and lymph nodes were taken from fresh cadavers, and the lymphocytes for injection into the horse were removed from these tissues in much the same way as must have been used by Metchnikoff two-thirds of a century earlier.

In June and July, 1966, the first patients in the world to be treated with ALG could be picked out of a crowd of their transplant peers at the Colorado General or Denver Veterans Administration Hospitals. The ALG was given into the muscles of the buttock and caused such severe pain and swelling that the patients constantly walked the floors trying to rid themselves of what felt like a charley horse. They sat crookedly on chairs and formed their own support group to exchange tall tales and especially complaints.

The trial was a success (97,98). Rejection was practically eliminated during the period of ALG therapy if treatment was started at the time of transplantation. If ALG treatment was delayed, it could be used effectively to reverse established rejection. The amounts of Imuran and prednisone (especially the latter) were reduced. This was the beginning of the triple-drug immunosuppression (Imuran-prednisone-ALG) which was the new plateau from which liver transplantation could start again. Not far behind would come the heart.

Later, improvements were made in ALG therapy. Purer preparations of human lymphocytes could be obtained by collecting them from the thoracic duct during thoracic duct drainage (Traeger of Lyon), from the thymus, or by culturing them. The technique of lymphocyte culture was developed by George Moore of Roswell Park Hospital, Buffalo and applied by John Najarian, Richard Condie, and Richard Simmons at the University of Minnesota. Also, the ALG could be given intravenously, eliminating the intramuscular injection pain which for some patients was almost unendurable.

The limitations of ALG were defined almost immediately (97-99). It was not a drug like Imuran or prednisone which could be used for chronic treatment because of immune reactions against the injected horse protein. A penalty for the use of ALG was a higher incidence of virus infections including those (Epstein-Barr) associated with lymphoma formation. What we had accomplished was a significant but not a quantum improvement in patient care.

Ben Cosimi, one of our Colorado medical students, assisted with the development of ALG for human use before leaving for the Massachusetts General Hospital in July 1964 to begin his surgical training. His dream of producing a more practical and safer ALG came within reach when Kohler and Milstein developed the hybridoma technology (100). With it, Gideon Goldstein and Cosimi produced OKT3, a modern version of ALG, and began its clinical use in 1980 (101).

Improved immunosuppression and a better understanding of tissue matching were justifications for resumption of clinical liver transplant trials. There remained the problems of the liver donor and liver preservation. Preservation technology for all organs began with liver transplant research in the late 1950s. The first innovation of core cooling by infusion of chilled lactated Ringer's solution into the portal vein was the most important (31). This was the first time hypothermia was induced by the intravascular infusion of cold fluids. Earlier it had been appreciated by cardiac surgeons that hypothermia protected ischemic tissue below the level of aortic-clamping (102). Hypothermia to protect human renal homografts was first accomplished with total body hypothermia of living volunteer donors (44), but before long we replaced this cumbersome and potentially dangerous method with infusion of chilled fluid into the kidney immediately after its removal (103). It was a simple and overdue transfer of technology from the laboratory.

Today, core cooling is the first step in the preservation of all whole organ cadaver grafts and this is most often done in situ by some variant of the technique observed by Goodwin (see earlier) in May 1963 during his visit to Colorado (56,57). This method for the continuous hypothermic perfusion of cadaveric livers and kidneys was used clinically long before the acceptance of brain death conditions. Later Ackerman and Snell (104) and Merkel, Jonasson, and Bergan (105) popularized in situ cooling of cadaveric kidneys with cold electrolyte solution infused into the distal aorta. Two decades later, in situ cooling was refined to allow removal of all thoracic and abdominal organs, including the liver, without jeopardizing any of the individual organs (106,107). When the final versions of these so-called flexible techniques of procurement were published in the 1980s, they quickly became a worldwide standard.

Extension of the safe period beyond that provided by initial cooling and avoidance of warm ischemia has followed one of two prototype strategies. The approach of providing a limited and continuous hypothermic circulation was refined to isolated organ perfusion by Ackerman and Barnard (108) who used a perfusate containing blood. The perfusate was oxygenated within a hyperbaric oxygen chamber. The same method with slight modifications also permitted the successful preservation of dog livers for as long as two days (109) and was applied clinically with remarkable success in several human cases in the pre-brain death era after preliminary total body cooling with extracorporeal perfusion (110).

The isolated liver perfusion project was headed by Larry Brettschneider, a 30-year-old surgeon and Lieutenant Commander in the United State Navy who was detached to Colorado for two years, beginning in early 1966. The technique was ready for clinical use by the end of the year. It may be that this was the best method of liver preservation used to the 1990s. However, the hyperbaric chamber was cumbersome and extremely heavy. The pilots who flew us in small planes to donor cities on the other side of the Rocky Mountains were terrified that it would roll through the side of the aircraft like a lead ball, or explode from its high internal pressure. Later, when brain death was accepted, it never was used again.

Yet, it played a role. This was the technique that was used to preserve all of the first successfully transplanted human livers in 1967 and 1968. Brettschneider died tragically in 1978. When Belzer et al (111) were able to eliminate the hemoglobin and hyperbaric chamber components for kidney preservation, their asanguinous perfusion technique became a worldwide standard. However, efforts to use this modification for livers were unsuccessful (112).

The alternative strategy for the preservation of kidneys, livers, and other organs after initial cooling also had its origin in this era. This was the instillation of special solutions such as that described by Collins, Bravo-Shugarman, and Terasaki (113) or the plasma-like Schalm solution eventually used by Calne (114). The original Collins solution, or modification of it, was used for almost two decades for the so-called "slush" techniques of kidney preservation. The experimental work of Benichou et al (115) and Wall et al (116) with the Collins and Schalm solutions preceded their first clinical use for livers in 1976 which opened up the possibility of organ sharing between cities, but within narrow time limitations.

The introduction of the UW solution was the first major development in liver preservation since then. The superiority of the UW solution to any of previous "conventional" solutions for preservation of liver and extrahepatic organs has been demonstrated in experimental test models (117) and quickly confirmed in clinical trials (118,119) during the late 1980s. The advance with the liver was then applied to other organs.

One other project of this phase developed a life of its own which continues to expand 25 years later. This was an exploration of the optimum conditions for the transplantation of an extra (auxilary) liver at some ectopic site, leaving the diseased native liver in place. Reexamination was required of the mysterious Eck fistula (portacaval shunt) and the possible interaction between pancreatic insulin and the liver which had been my entry point into transplantation in 1956 (see earlier). The liver shrinkage caused by portacaval shunts in dogs [and also in rats, baboons, and humans (120)] and the wasting, hair loss and brain damage that follow were ascribed until the mid 1960s to the loss of portal blood flow rather than the loss of exposure to the liver of any specific substance(s) in the portal blood (121-123). This became known as the flow hypothesis of portal physiology. Yet, an uneasiness about this glib explanation could be sensed in an otherwise authoritarian review article written in 1961 by J. L. Bollman of the Mayo Clinic (124) who wrote, "In the 83 years since it was first reported the Eck fistula has been reasonably successful in hiding its secrets as well as giving rise to many additional questions fundamental to an understanding of the functions of the intestine, liver and brain."

The secrets referred to by Bollman finally were unmasked by auxiliary liver transplant studies in dogs which were begun in 1963. This operation was described in 1955 by Welch in what was the first mention of liver transplantation in the medical literature (125). Our experiments eight years later showed that coexisting livers competed with each other for some substrate(s) or nutritional substance(s) (57,126). From 1963 onward, it was clear that when two livers were present, the one with primary access to portal venous flow would thrive because it consumed something in the portal blood, whereas the other liver would atrophy. This dictated the technical conditions for auxiliary liver grafts. Their portal venous inflow would require blood from the splanchnic venous bed. It was concluded that portal blood contained "hepatotrophic" factors, but the identity of these mysterious substances was unknown at first.

To find out, definitive non-transplant experimental models were designed in which the animal's own liver was divided into two parts, each of which could be given the venous blood that came from different organs or different parts of the body (127-131). Later, experiments were done in which the effect on the liver of removing these organs was tested. All of the testing done from 1971 onward showed that the most potent (although not the only) hepatotrophic factors were from the pancreas. In the end, it was demonstrated that insulin when injected alone into the altered liver circulation could prevent the atrophy and most of the consequences to the liver that were caused by the Eck fistula (132).

This was the death blow to the portal flow hypothesis and the beginning of a new concept about the interactions of the liver with the pancreas and other abdominal organs. The role of insulin as a liver growth control factor was established, as well as a new field of hepatotrophic physiology (133). The concept was that the pancreas (particularly its insulin) and other less important but cumulatively significant substances from the viscera modulated hepatic structure, function, and capacity for regeneration. The metabolic interrelationships of intraabdominal organs was to become a consideration in the technical planning for transplantation of any of these organs and particularly the transplantation of multiple abdominal viscera. Ultimately, the multivisceral operation which had evoked bemusement in 1960 (36,37) became the starting point for variations which permitted the successful transplantation of bowel for the first time (134-136).

In addition, the original experimental techniques developed to uncover the insulin effects were applied almost two decades later to show that cyclosporine and FK 506 also have hepatotrophic properties including the augmentation of hepatic regeneration (137-139). These drugs and others including rapamycin bind to ubiquitous small molecular weight cytosolic proteins called immunophilins (140,141) and are thought to act by disrupting normal signal transduction pathways (142), but not only in cells with immunologic function (139). Recognition of the pleiotropic function (including growth control) of the immunophilin network (139,142,143) is the latest example of a ripple (or tidal wave) effect in basic science laboratories of clinically directed research in transplantation.

During 1964 to 1966, the Denver VA Hospital laboratory was like Grand Central Station. One visitor, Chris Barnard, was no casual tourist. Barnard spent the better part of a year in the United States at three centers: in Richmond with Dick Lower and Dave Hume who told me later that Barnard had seemed interested mainly in learning how to treat rejection, in Colorado (autumn 1966) where he focused his attention on the ALG project, and in Palo Alto where he visited Shumway whom he had known since their earlier days at the University of Minnesota. I told Barnard candidly that we were planning to go ahead with heart transplantation in Denver but not until we were successful with the liver. I assumed that he was going to start a kidney program in Capetown and so did the others whom he visited.

PHASE V (1967 to 1969)

With the support struts of Phase V in place, the time had come to resume the clinical trials of orthotopic liver transplantation (liver replacement). Procurement of livers was from "heart dead" donors. All of the recipients had triple-drug immunosuppression with Imuran, prednisone, and ALG. The seven new patients (all children) passed through the lethal period encountered during and just after liver transplantation in the 1963 cases. Four died after two, three and one-half, four and one-third, and six months. All other complications were trivial compared to the one which caused their deaths. This was the development of gangrene of a portion of the transplanted livers, the other part of which continued to function properly. The dead portion of the liver was infected with bacteria normally found in the intestine.

The other three children remained alive for 13, 15, and 30 months, long enough to demonstrate convincingly the potential value of this kind of treatment (144). Two of the three late deaths were caused by recurrence of the hepatomas which had been the reason for the transplantation; the third died of chronic rejection. By the time the last patient died, another child was a half year into a new life that now is well into the twenty-second posttransplant year (145). This recipient had biliary atresia but in her removed liver was found a small cancer which had not been suspected in advance. It never came back.

Carl Groth of Stockholm helped operate on and care for all of these patients. Before he returned to Sweden in March 1968, he helped complete an investigation in dogs (146) which was based on his observations in the children who developed partial gangrene of the liver graft. The study showed that an important factor predisposing to liver infection was undertreatment with immunosuppression with consequent rejection. In turn, a reduction in liver blood flow caused by rejection previously had been demonstrated by Groth (147), to set the stage for oxygen starvation of the transplanted liver and a consequent lowered resistance to bacteria. Paradoxically, the best way to prevent this was more vigorous antirejection treatment in spite of the consequent depression of systemic resistance to infection (148).

The prolonged survival of the first children in the series became known worldwide by September 1967. The ripple effect went beyond the liver. Penetration of the barrier which had precluded extension of transplantation operations beyond the relatively simple kidney fanned the embers in other organ-defined specialities. By the end of the year, Barnard of Capetown had performed the first heart transplantation (149), followed shortly by the beginning of Shumway's clinical program at Stanford (150). Responding to phone call requests, we became the suppliers of homemade ALG for these and other heart programs which followed.

Within a year, the first successful lung transplantation was performed by Derom of Louvain (151) and the first pancreas and intestinal transplants were attempted by Lillehei and Kelly of the University of Minnesota (152,153). Most of the attempts with all of the extrarenal organs failed. When the rush of enthusiasm was replaced by reality, only a few diehards were left. Further clinical development of hearts would be at Stanford. The pancreas would depend upon Carl Groth in Stockholm, Jean M. Dubernard of Lyon, and Dave Sutherland of Minneapolis. Lung transplantation lay dormant for almost 15 years until Joel Cooper of Toronto finally established its practicality. Intestinal transplantation was abandoned for almost two decades.

Liver transplantation continued in Cambridge (Calne) and Denver. By early February 1969 we had treated 20 patients since the 1967 reinstitution of the liver replacement trials. For one, a chimpanzee was the donor. Only seven of the patients survived for more than one year. The conclusion was inescapable. Liver transplantation was a feasible but impractical way to treat end stage liver disease. This was the picture presented in a second book, *Experience in Hepatic Transplantation* (154), a companion piece to the earlier *Experience in Renal Transplantation* (61). The liver book was written with Charley Putnam, then a senior medical student at Northwestern and now a Professor of Surgery (in the same department as Charlie Zukowski) at the University of Arizona.

In the new book, every known clinical attempt made at liver transplantation in the world (orthotopic and auxiliary) and every experimental paper written on the subject up to early 1969 were included. The book portrayed liver transplantation more pessimistically than it would actually be during the following 10 years. Yet, more recipients died than lived throughout this time. Altogether, 170 patients were treated between 1963 and the end of 1979 (145). Only 29 (16.5 percent) still survive. Now, they are 11 to 21 and one-half years posttransplantation. In England, Calne maintained the only other sustained liver transplant program which was opened in May 1967 (155). As in Colorado, these efforts created controversy. Calne became a European voice in the wilderness.

PHASE VI (1970 -)

If it had not been for the 1960s, transplantation would have remained a fancy, and if it were not for the 1980s, it would have remained a starveling. In between was the time for those thousands of details to be clarified which had been skipped in the rush to the finish line; a time to explain why the beachhead known as transplantation had become a slowly eroding revetment; and a time to look for something better. ALG had had a smaller than expected impact on transplantation worldwide because of the necessity for its temporary use only and because of problems with its manufacture, standardization, and testing. Only about 15 percent of cadaver kidney transplantations worldwide were done with ALG treatment.

The results with cadaver kidney transplantation remained fixed at an unsatisfactory level (64,156-158). Trapped now by their own partially successful efforts, surgeons interested in the extrarenal organs brooded in their self-made dungeons, smuggling messages to each other or communicating by secret signals, tapped on their academic cell walls. There were very few left who continued to try. Then the way out of the dilemma came with cyclosporine. The drug was discovered by workers at the Sandoz Corporation and shown by Jean Borel to weaken immunologic responses in a variety of test systems including that of skin graft rejection in mice (159).

In England, Calne and his Cambridge team evaluated cyclosporine for the transplantation of a variety of whole organs (kidney, heart, liver, pancreas) in rats, dogs, and pigs. These experiments led directly to the first human trials in kidney transplantation at Cambridge, beginning in the late spring of 1978 (160,161). At first, it was hoped that cyclosporine could be used as single-drug therapy, but it too was destined to be part of cocktail regimens in which steroids were the most dose maneuverable component (162) and to which azathioprine, ALG, and other agents could be added. Cadaver kidney transplantation finally reached the level of a legitimate clinical service. Transplantation of the liver (145,163) and soon after the other extrarenal organs was revolutionized overnight. For me, most of this new era was at the University of Pittsburgh, where I moved in December 1980. Liver transplantation was made easier by a modern day version of veno-venous bypass (145,164,165). The liver and heart transplant gold rush dwarfed what had happened with the kidney in 1964.

With the revolution came a downside. In addition to its marvelous qualities, cyclosporine had side effects which had been described by Calne as early as 1979 (161). The most serious were nephrotoxicity and hypertension in the majority of recipients of all kinds of organs. Nephrotoxicity, hirsutism, gum hyperplasia, neurotoxicity, and other less serious side effects were dose-related. When the doses were reduced to relieve them, the risk of rejection increased. Transplant surgeons with an obsession for perfection were less interested in working around these problems than in finding a more fundamental solution. FK 506, a macrolide antibiotic which was discovered in 1984 and first reported in 1987 (166-168) is the most promising new agent. Extensive clinical trials were begun in 1989 (169).

With the advances of the last decade, it has become possible to improve the kinds of transplantation (liver, heart, pancreas) which were feasible but not practical and to succeed with previously "forbidden" transplants of pancreatic islets (170), intestine (171,172), and multivisceral organs containing intestine (134-136). The relative "acceptance" of solid organ grafts in many patients still is not understood, but a recent clue has been the demonstration of postoperative lymphoreticular repopulation of human intestinal grafts with recipient cells.

This means that transplanted organs can become "composites," possibly helping to explain why the need for chronic immunosuppression may recede in successful clinical transplantation of all organs, not just those which are rich in lymphoid tissue. Such cell repopulation was first noted by Porter more than two decades ago in the macrophage system of human liver homografts (89). Thirty years ago, in describing what they called graft adaptation, Michael and Hazel Woodruff had asked if thyroid transplants underwent some kind of change which explained their acceptance by the host if they could be protected from rejection at the outset (173).

In hepatic grafts whose composite structure has been known for more than two decades (89), it was established in 1964 (58) that the graft metabolic specificity was retained as shown by the replacement of recipient haptoglobin phenotypes with those of the donor. This simple observation was the basis for the treatment with liver transplantation of numerous inborn errors of metabolism, now numbering nearly two dozen (174). The metabolic correction lasts for the lifetime of the graft. Every few months, a new disease is added to the list.

Now half-forgotten ideas were being reexplored, and burned-out camp sites were being rediscovered, as had occurred with those who arrived in the 1950s. When mountains are climbed by different people, the triumph can be spoiled by asking who took the first step to the summit, who took the longest stride, and most insidiously who did not. All of those who made the clinical transplant journey of the last 40 years found footprints, which like those in the snow in the high mountain reaches, do not melt. No matter how early the transplant explorer's arrival, someone already had been there, at least part way.

REFERENCES

1. Starzl TE. Personal reflections in transplantation. Surg Clin North Am 1978; 58:879.
2. Starzl TE. The landmark identical twin case. JAMA 1984; 251:2572.
3. Starzl TE. The development of clinical renal transplantation. Am J Kidney Dis 1990; 26:548.
4. Calne RY. Organ Transplantation: from laboratory to clinic (Lister Oration). Br Med J 1985; 291:1751.
5. Calne RY. Recollections from the laboratory to the clinic. In: Terasaki PI, Ed. History of Transplantation. Los Angeles, UCLA Tissue Typing Laboratory 1991.
6. Murray JE. Discovery: Reflections on the first successful kidney transplantation. World J Surg 1982; 6:372.
7. Moore FD. Give and Take. The Development of Tissue Transplantation. Philadelphia, WB Saunders Company and Garden City, New York, Doubleday and Company, 1964.
8. Groth CG. Landmarks in clinical renal transplantation. Surg Gynecol Obstet 1972; 134:323.
9. Kahan BD. Transplantation timeline. Transplantation 1991; 51:1.
10. Hau T. In: Landes RG, Ed. Clio Chirurgica: Renal Transplantation Silvergirl Inc., Austin, Texas 1991.
11. Jaboulay M. Greffe du reins au pli du conde par soudures arterielles et veineuses. (Kidney grafts in the antecubital fossa by arterial and venous anastomosis). Lyon Medical 1906; 107:575.
12. Unger E. Nierentransplantation. (Kidney transplantation). Wien Klin Wochenschr 1910; 47:573.
13. Voronoy Yu Yu. Sobre el bloqueo del aparato reticuloendotelial del hombre en algunas formas de intoxicacion por el sublimado y sobre la transplantacion del rinon cadaverico como metodo de tratimiento de la anuria consecutiva a aquella intoxicacion. (Blocking the reticuloendothelial system in man in some forms of mercuric chloride intoxication and the transplantation of the cadaver kidney as a method of treatment for the anuria resulting from this intoxication). El Siglo Medico 1937; 97:296.
14. Dubost C, Oeconomos N, Nenna A, Milliez P. Resultats d'une tentative de greffe

renale. Bull Soc Med Hop Paris 1951; 67:1372.

15. Kuss R, Teinturier J, Milliez P. Quelques essais de greffe rein chez l'homme. Mem Acad Chir 1951; 77:755.
16. Servelle M, Soulie P, Rougeulle J. Greffe d'une rein de supplicie a une malade avec rein unique congenital, atteinte de nephrite chronique hypertensive azatemique. Bull Soc Med Hop Paris 1951; 67:99.
17. Hume DM, Merrill JP, Miller BF, Thorn GW. Experience with renal homotransplantation in the human: Report of nine cases. J Clin Invest 1955; 34:327.
18. Lawler RH, West JW, McNulty PH, et al. Homotransplantation of the kidney in the human. JAMA 1950; 144:844.
19. Meyer WH Jr, Starzl TE. The effect of Eck and reverse Eck fistula in dogs with experimental diabetes mellitus. Surgery 1959; 45:760.
20. Starzl TE, Butz GW Jr, Meyer WH Jr, et al. Effect in dogs of various portal vein shunts on response to insulin. Am J Physiol 1962; 203:275.
21. Starzl TE, Scanlan WA, Yanof HM, et al. A comparison of the hypoglycemic effect of insulin with systemic venous and portal venous administration. J Surg Res 1963; 3:293.
22. Starzl TE, Scanlan WA, Thornton FH, et al. Effect of insulin on glucose metabolism in the dog after portacaval transposition. Am J Physiol 1965; 209:221.
23. Starzl TE, Bernhard VM, Benvenuto R, Cortes N. A new method for one-stage hepatectomy in dogs. Surgery 1959; 46:880.
24. Merrill JP, Murray JE, Harrison JH, Guild WR. Successful homotransplantation of the human kidney between identical twins. JAMA 1956; 160:277.
25. Medawar PB. The behavior and fate of skin autografts and skin homografts in rabbits. J Anat 1944; 78:176.
26. Medawar PB. Second study of behavior and fate of skin homografts in rabbits. J Anat 1945; 79:157.
27. Billingham RE, Krohn PL, Medawar PB. Effect of cortisone on survival of skin homografts in rabbits. Br Med J 1951; 1:1157.
28. Krohn PL. The effect of cortisone on second set skin homografts in rabbits. Br J Exp Pathol 1954; 35:539.
29. Dempster WJ. The effect of cortisone on the homotransplanted kidney. Arch Int Pharmacodynther 1953; 96:253.
30. Dempster WJ, Lennox B, Boag JW. Prolongation of survival of skin homotransplants in the rabbit by irradiation of the host. Br J Exp Pathol 1950; 31:670.
31. Starzl TE, Kaupp HA Jr, Brock DR, et al. Reconstructive problems in canine liver homotransplantation with special reference to the postoperative role of hepatic venous flow. Surg Gynecol Obstet 1960; 111:733.
32. Moore FD, Wheeler HB, Demissianos HV, et al. Experimental whole-organ transplantation of the liver and of the spleen. Ann Surg 1960; 152:374.
33. Starzl TE. Discussion of Moore FD, Wheeler HB, Demissianos HV, et al. Experimental whole-organ transplantation of the liver and of the spleen. Ann Surg 1960; 152:386.
34. Starzl TE, Kaupp HA Jr, Brock DR, Linman JW. Studies on the rejection of the transplanted homologous dog liver. Surg Gynecol Obstet 1961; 112:135.
35. Hume DM, Benjamin T, Jackson, et al. The homotransplantation of kidneys and of fetal liver and spleen after total body irradiation. Ann Surg 1960; 152(3):354.

36. Starzl TE, Kaupp HA Jr. Mass homotransplantation of abdominal organs in dogs. Surg Forum 1960; 11:28.

37. Starzl TE, Kaupp HA Jr, Brock DR, et al. Homotransplantation of multiple visceral organs. Am J Surg 1962; 103:219.

38. Monchik GJ, Russell PS. Transplantation of the small bowel in the rat: technical and immunologic considerations. Surgery 1971; 70:693.

39. Starzl TE, Butz GW Jr, Brock DR, et al. Canine liver homotransplants: The effect of host and graft irradiation. Arch Surg 1962; 85:460.

40. Calne RY. Rejection of renal homografts: inhibition in dogs by 6-mercaptopurine. Lancet 1960; 1:417.

41. Zukoski CF, Lee HM, Hume DM. The prolongation of functional survival of canine renal homografts by 6-mercaptopurine. Surg Forum 1960; 11:470.

42. Meeker W, Condie R, Weiner D, et al. Prolongation of skin homograft survival in rabbits by 6-mercaptopurine. Proc Soc Exp Biol Med 1959; 102:459.

43. Schwartz R, Dameshek W. The effects of 6-mercaptopurine on homograft reactions. J Clin Invest 1960; 39:952.

44. Starzl TE, Brittain RS, Stonnington OG, et al. Renal transplantation in identical twins. Arch Surg 1963; 86:600.

45. They Decide Who Lives, Who Dies, Life Magazine 1962; Nov 9, 53 (No.19):102.

46. Kuss R, Legrain M, Mathe G, et al. Homology human kidney transplantation. Experience with six patients. Postgrad Med J 1962; 38:528.

47. Hamburger J, Vaysse J, Crosnier J, et al. Renal homotransplantation in man after radiation of the recipient. Am J Med 1962; 32:854.

48. Murray JE, Merrill JP, Dammin GJ, et al. Study of transplantation immunity after total body irradiation: Clinical and experimental investigation. Surgery 1960; 48:272.

49. Murray JE, Merrill JP, Dammin GJ, et al. Kidney transplantation in modified recipients. Ann Surg 1962; 156:337.

50. Marchioro TL, Axtell HK, LaVia MF, et al. The role of adrenocortical steroids in reversing established homograft rejection. Surgery 1964; 55:412.

51. Starzl TE, Marchioro TL, Waddell WR. The reversal of rejection in human renal homografts with subsequent development of homograft tolerance. Surg Gynecol Obstet 1963; 117:385.

52. Calne RY, Murray JE. Inhibition of the rejection of renal homografts in dogs by Burroughs Wellcome 57-322. Surg Forum 1961; 12:118.

53. Waddell W. Discussion of Hume DM, Magee JH, Kauffman HM Jr, et al. Renal homotransplantation in man in modified recipients. Ann Surg 1963; 158:642.

54. Goodwin WE, Kaufman JJ, Mims MM, et al. Human renal transplantation. I. Clinical experiences with six cases of renal homotransplantation. J Urology 1963; 89:13.

55. Starzl TE, Putnam CW, Halgrimson CG, et al. Cyclophosphamide and whole organ transplantation in human beings. Surg Gynecol Obstet 1971; 133:981.

56. Marchioro TL, Huntley RT, Waddell WR, Starzl TE. Extracorporeal perfusion for obtaining postmortem homografts. Surgery 1963; 54:900.

57. Starzl TE, Marchioro TL, Von Kaulla KN, et al. Homotransplantation of the liver in humans. Surg Gynecol Obstet 1963; 117:659.

58. Starzl TE, Marchioro TL, Rowlands DT Jr, et al. Immunosuppression after experimental and clinical homotransplantation of the liver. Ann Surg 1964; 160:411.

59. Moore FD, Birtch AG, Dagher F, et al. Immunosuppression and vascular insufficiency in liver transplantation. Ann NY Acad Sci 1964; 102:729.

60. Demirleau, Noureddine, Vignes, Prawerman, Reziciner, Larraud, Louviers. Tentative d'homogreffe hepatique (Attempted hepatic homograft). Mem Acad Chir (Paris) 1964; 90:177.

61. Starzl TE. Experience in Renal Transplantation WB Saunders Company, Philadelphia, 1964.

62. Murray JE, Gleason R, Bartholomay A. Second report of registry in human kidney transplantation. Transplantation 1964; 2:660.

63. Starzl TE, Schroter GPJ, Hartmann NJ, et al. Long term (25 year) survival after renal homotransplantation - the world experience. Transplant Proc 1990; 22:2361.

64. Opelz G, Mickey MR, Terasaki P. HLA matching and cadaver transplant survival in North America. Transplantation 1977; 23:470.

65. Hitchcock CR, Kiser JC, Telander RL, Seljoskog EL. Baboon renal grafts. JAMA 1964; 189:934.

66. Reemtsma K, McCracken BH, Schlegel JU, et al. Renal heterotransplantation in man. Ann Surg 1964; 160:384.

67. Starzl TE, Marchioro TL, Peters GN, et al. Renal heterotransplantation from baboon to man: Experience with 6 cases. Transplantation 1964; 2:752.

68. Bailey L, Nehlsen-Cannarella S, Concepcion W, Jolley W. Baboon to human cardiac xenotransplantation in a neonate. JAMA 1985; 254:3321.

69. Hardy M, Ed. In: Xenograft 25, Proceedings of the International Congress on Xenograft 25 held at Arden House, Harriman, New York, November 11-13, 1988, Amsterdam and New York, Excerpta-Medica 1989.

70. Starzl TE. Discussion of Murray JE, Wilson RE, et al. Five years' experience in renal transplantation with immunosuppressive drugs: survival, function, complications, and the role of lymphocyte depletion by thoracic duct fistula. Ann Surg 1968; 168:434.

71. Penn I, Hammond W, Brettschneider L, Starzl TE. Malignant lymphomas in transplantation patients. Transplant Proc 1969; 1:106.

72. Starzl TE, Penn I, Putnam CW, et al. Iatrogenic alterations of immunologic surveillance in man and their influence on malignancy. Transplant Rev 1971; 7:112.

73. Starzl TE, Nalesnik MA, Porter KA, et al. Reversibility of lymphomas and lymphoproliferative lesions developing under cyclosporin-steroid therapy. Lancet 1984; 1:583.

74. Starzl TE, Marchioro TL, Holmes JH, Waddell WR. The incidence, cause, and significance of immediate and delayed oliguria or anuria after human renal transplantation. Surg Gynecol Obstet 1964; 119:819.

75. Starzl TE, Tzakis A, Makowka L, et al. The definition of ABO factors in transplantation: Relation to other humoral antibody states. Transplant Proc 1987; 19:4492.

76. Dausset J. The HLA Adventure. In: Terasaki PI, Ed. History of HLA: Ten recollections. UCLA Tissue Typing Laboratory, Los Angeles, California, 1990; 1.

77. Starzl TE, Marchioro TL, Terasaki PI, et al. Chronic survival after human renal homotransplantations: Lymphocyte-antigen matching, pathology and influence of thymectomy. Ann Surg 1965; 162:749.

78. Terasaki PI, Vredevoe DL, Mickey MR, et al. Serotyping for homotransplantation. VI. Selection of kidney donors for thirty-two recipients. Ann NY Acad Sci 1966; 129:500.

79. Starzl TE, Porter KA, Andres G, et al. Long-term survival after renal transplantation in humans: With special reference to histocompatibility matching. thymectomy, homograft glomerulonephritis, heterologous

ALG, and recipient malignancy. Ann Surg 1970; 172:437.

80. Gjertson D, Terasaki P, Takamoto S. National allocation of cadaveric kidneys by HLA matching: projected effect on outcome and costs. N Engl J Med 1991; 324:1032.

81. Terasaki PI, Marchioro TL, Starzl TE. Serotyping of human lymphocyte antigens: Preliminary trials on long-term kidney homograft survivors. In: Russell PS, Winn HJ, Amos DB, Eds: Histocompatibility Testing 1965. Washington DC, National Academy of Science, 1965; 83.

82. Starzl TE, Lerner RA, Dixon FJ, et al. Schwartzman reaction after human renal transplantation. N Engl J Med 1968; 278:642.

83. Starzl TE. Precepts of renal homotransplantation applied to homografting of other organs. In: Experience In Renal Transplantation WB Saunders Company, Philadelphia, 1964; 360.

84. Starzl TE, Marchioro TL, Porter KA, et al. Factors determining short- and long-term survival after orthotopic liver homotransplantation in the dog. Surgery 1965; 58:131.

85. Starzl TE, Putnam CW. Experience in Hepatic Transplantation. Philadelphia, WB Saunders Company, 1969; 203.

86. Cordier G, Garnier H, Clot JP, et al. La greffe de foie orthotopique chez le porc. Mem Acad Chir (Paris) 1966; 92:799.

87. Peacock JH, Terblanche J. Orthotopic homotransplantation of the liver in the pig. In: Read AE, Ed. The Liver. Butterworth & Co., Ltd. London, 1967; 333.

88. Calne RY, White HJO, Yoffa DE, et al. Observations of orthotopic liver transplantation in the pig. Br Med J 1967; 2:478.

89. Porter KA. Pathology of the orthotopic homograft and heterograft. In: Experience in Hepatic Transplantation. WB Saunders Company, Philadelphia, 1969; 422.

90. Metchnikoff E. Etudes sur la resorption des cellules. Ann Inst Pasteur (Paris) 1899; 13:737.

91. Waksman BH, Arbouys S, Arnason BG. The use of specific "lymphocyte antisera" to inhibit hypersensitive reactions of the delayed type. J Exp Med 1961; 114:997.

92. Woodruff MFA, Anderson NF. Effect of lymphocyte depletion by thoracic duct fistula and administration of anti-lymphocytic serum on the survival of skin homografts in rats. Nature (London) 1963; 200:702.

93. Monaco AP, Wood ML, Russell PS. Effect of adult thymectomy on the recovery from immunologic depression induced by heterologous antilymphocyte serum. Science 1965; 149:423.

94. Medawar PB. Biological effects of heterologous antilymphocyte sera. In: Rapaport F, Dausset J, Eds. Human Transplantation. New York, Grune & Stratton, Inc., 1968; 501.

95. Iwasaki Y, Porter KA, Amend J, et al. The preparation and testing of horse antidog and antihuman antilymphoid plasma or serum and its protein fractions. Surg Gynecol Obstet 1967; 124:1.

96. Kashiwagi N, Sherer D, Townsend CM, et al. Antibody localization in horse, rabbit, and goat antilymphocyte sera. Surgery 1970; 67:789.

97. Starzl TE, Marchioro TL, Porter KA, et al. The use of heterologous antilymphoid agents in canine renal and liver homotransplantation, and in human renal homotransplantation. Surg Gynecol Obstet 1967; 124:301.

98. Starzl TE, Groth CG, Terasaki PI, et al. Heterologous antilymphocyte globulin, histocompatibility matching, and human renal homotransplantation. Surg Gynecol Obstet 1968; 126:1023.

99. Starzl TE, Putnam CW. Efforts to mitigate or preventrejection. In: Experience in Hepatic Transplantation. WB Saunders Company, Philadelphia, 1969; 193.

100. Kohler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. Nature 1975; 256:495.

101. Cosimi AB, Burton RC, Colvin RB, et al. Treatment of acute renal allograft rejection with OKT3 monoclonal antibody. Transplantation 1981; 32:535.

102. Owens TC, Prevedel AE, Swan H. Prolonged experimental occlusion of thoracic aorta during hypothermia. Arch Surg 1955; 70:95.

103. Starzl TE. Experience In Renal Transplantation, WB Saunders Company, Philadelphia, 1964; 68.

104. Ackerman JR, Snell ME. Cadaveric renal transplantation. Br J Urol 1968; 40:515.

105. Merkel FK, Jonasson O, Bergan JJ. Procurement of cadaver donor organs: evisceration technique. Transplant Proc 1972; 4:585.

106. Starzl TE, Hakala TR, Shaw BW Jr, et al. A flexible procedure for multiple cadaveric organ procurement. Surg Gynecol Obstet 1984; 158:223.

107. Starzl TE, Miller C, Broznick B, Makowka L. An improved technique for multiple organ harvesting. Surg Gynecol Obstet 1987; 165:343.

108. Ackerman JR, Barnard CN. A report on the successful storage of kidneys. Br J Surg 1966; 53:525.

109. Brettschneider L, Daloze PM, Huguet C, et al. The use of combined preservation techniques for extended storage of orthotopic liver homografts. Surg Gynecol Obstet 1968; 126:263.

110. Starzl TE, Putnam CW. Donor Hepatectomy and Liver Preservation. In: Experience in Hepatic Transplantation. Philadelphia, WB Saunders Company, 1969; 41.

111. Belzer FO, Ashby BS, Dunphy JE. 24-hour and 72-hour preservation of canine kidneys. Lancet 1967; 2:536.

112. Brettschneider L, Groth CG, Starzl TE. Experimental and clinical preservation of liver homografts. In: Norman JC, Folkman J, Hardison WG, et al, Eds. Organ Perfusion and Preservations. Appleton-Century-Crofts, New York, 1968; 271.

113. Collins GM, Bravo-Shugarman M, Terasaki PI. Kidney preservation for transportation: Initial perfusion and 30 hours ice storage. Lancet 1969; 2:1219.

114. Schalm SW. A simple and clinically applicable method for the preservation of a liver homograft. Thesis, University of Leyden, Holland, 1968.

115. Benichou J, Halgrimson CG, Weil R III, et al. Canine and human liver preservation for 6 to 18 hours by cold infusion. Transplantation 1977; 24:407.

116. Wall WJ, Calne RY, Herbertson BM, et al. Simple hypothermic preservation for transporting human livers long distances for transplantation. Transplantation 1977; 23:210.

117. Jamieson NV, Sundberg R, Lindell S, et al. Successful 24- to 30-hour preservation of the canine liver: A preliminary report. Transplant Proc 1988; 20(Suppl 1):945.

118. Kalayoglu M, Sollinger WH, Stratta RJ, et al. Extended preservation of the liver for clinical transplantation. Lancet 1988; 1:617.

119. Todo S, Nery J, Yanaga K, et al. Extended preservation of human liver grafts with UW solution. JAMA 1989; 261:711.

120. Putnam CW, Porter KA, Starzl TE. Hepatic encephalopathy and light and electron micrographic changes of the baboon liver after portal diversion. Ann Surg 1976; 184:155.

121. Mann FC. The William Henry Welch Lectures: II. Restoration and pathologic reactions of the liver. J Mt Sinai Hosp 1944; 11:65.

122. Child CG, Barr D, Holswade GR, Harrison C. Liver regeneration following portacaval

transposition in dogs. Ann Surg 1953; 138:600.

123. Fisher B, Russ C, Updegraff H, Fisher E. Effect of increased hepatic blood flow upon liver regeneration. Arch Surg 1954; 69:263.

124. Bollman JL. The animal with an Eck fistula. Physiol Rev 1961; 41:607.

125. Welch CS. A note on transplantation of the whole liver in dogs. Transplant Bull 1955; 2:54.

126. Marchioro TL, Porter KA, Dickinson TC, et al. Physiologic requirements for auxiliary liver homotransplantation. Surg Gynecol Obstet 1965; 121:17.

127. Marchioro TL, Porter KA, Brown BI, et al. The effect of partial portacaval transposition on the canine liver. Surgery 1967; 61:723.

128. Starzl TE, Francavilla A, Halgrimson CG, et al. The origin, hormonal nature, and action of hepatotrophic substances in portal venous blood. Surg Gynecol Obstet 1973; 137:179.

129. Starzl TE, Lee IY, Porter KA, Putnam CW. The influence of portal blood upon lipid metabolism in normal and diabetic dogs and baboons. Surg Gynecol Obstet 1975; 140:381.

130. Starzl TE, Porter KA, Kashiwagi N, et al. The effect of diabetes mellitus on portal blood hepatotrophic factors in dogs. Surg Gynecol Obstet 1975; 140:549.

131. Starzl TE, Porter KA, Kashiwagi N, Putnam CW. Portal hepatotrophic factors, diabetes mellitus, and acute liver atrophy, hypertrophy and regeneration. Surg Gynecol Obstet 1975; 141:843.

132. Starzl TE, Watanabe K, Porter KA, Putnam CW. Effect of insulin, glucagon, and insulin/glucagon infusion on liver morphology and cell division after complete portacaval shunt in dogs. Lancet 1976; 1:821.

133. Starzl TE, Porter KA, Francavilla A. The Eck fistula in animals and humans. Curr Probl Surg 1983; 20:687.

134. Starzl TE, Rowe M, Todo S, et al. Transplantation of multiple abdominal viscera. JAMA 1989; 26:1449.

135. Grant D, Wall W, Mimeault R, et al. Successful small-bowel/liver transplantation. Lancet 1990; 335:181.

136. Starzl TE, Todo S, Tzakis A, et al. The many faces of multivisceral transplantation. Surg Gynecol Obstet 1991; 172:335.

137. Makowka L, Svanas G, Esquivel C, et al. The effect of cyclosporine on hepatic regeneration. Surg Forum 1986; 37:352.

138. Francavilla A, Barone M, Todo S, et al. Augmentation of rat liver regeneration by FK 506 compared with cyclosporine. Lancet 1989; 1:1248.

139. Starzl TE, Porter KA, Mazzaferro V, et al. Hepatotrophic effects of FK 506 in dogs. Transplantation 1991; 51:67.

140. Harding MW, Galat A, Uehling DE, Schreiber SL. A receptor for the immunosuppressant FK 506 is a cis-trans peptidyl-prolyl isomerase. Nature 1989; 341:758.

141. Siekierka JJ, Hung SHY, Poe M, et al. A cytosolic binding protein for the immunosuppressant FK 506 has peptidyl-prolyl isomerase activity but is distinct from cyclophilin. Nature 1989; 341:755.

142. Schreiber SL. Chemistry and biology of the immunophilins and their immunosuppressive ligands. Science 1991; 251:283.

143. Starzl TE, Fung JJ, Todo S. Contempo 90: Transplantation. JAMA 1990; 263:2686.

144. Starzl TE, Groth CG, Brettschneider L, et al. Orthotopic homotransplantation of the human liver. Ann Surg 1968; 168:392.

145. Starzl TE, Iwatsuki S, Van Thiel DH, et al. Evolution of liver transplantation. Hepatology 1982; 2:614.

146. Brettschneider L, Tong JL, Boose DS, et al. Specific bacteriologic problems after or-

thotopic liver transplantation in dogs and pigs. Arch Surg 1968; 97:313.

147. Groth CG, Porter KA, Otte JB, et al. Studies of blood flow and ultrastructural changes in rejecting and nonrejecting canine orthotopic liver homografts. Surgery 1968; 63:658.

148. Starzl TE. Infectious complications, excluding partial hepatic gangrene. In: Experience in Hepatic Transplantation, W.B. Saunders Co., Philadelphia, 1969; 329.

149. Barnard CN. What we have learned about heart transplants. J Thorac Cardiovasc Surg 1968; 56:457.

150. Stinson EB, Dong E, Jr., Schroeder JS, et al. Initial clinical experience with heart transplantation. Am J Cardiol 1968; 22:791.

151. Derom F, Barbier F, Ringoir S, et al. Ten-month survival after lung homotransplantation in man. J Thorac Cardiovasc Surgery 1971; 61:835.

152. Kelly WD, Lillehei RC, Merkel FK, et al. Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy. Surgery 1967; 61:827.

153. Lillehei RC, Idezuki Y, Feemster JA, et al. Transplantation of stomach, intestine, and pancreas: Experimental and clinical observations. Surgery 1967; 62:721.

154. Starzl TE, Putnam CW. Experience in Hepatic Transplantation, Philadelphia, WB Saunders Company, 1969; 1.

155. Calne RY, Williams R. Liver transplantation in man. I. Observations on technique and organization in five cases. Br Med J 1968; 4:535.

156. Tilney NL, Storm TB, Vineyard GC, Merrill JP. Factors contributing to the decline mortality rate in renal transplantation. N Engl J Med 1978; 299:1321.

157. Najarian JS, Sutherland DER, Simmons, RL, et al. Ten year experience with renal transplantation in juvenile onset diabetics. Ann Surg 1979; 190:487.

158. Ascher NL, Ahrenholz DH, Simmons RL, Najarian JS. 100 second-renal allografts from a single transplantation institution. Transplantation 1979; 27:30.

159. Borel JF, Feurer C, Gubler HU, Stahelin H. Biological effects of cyclosporin A: A new antilymphocytic agent. Agents Actions 1976; 6:468.

160. Calne RY, White DJH, Thiru S, et al. Cyclosporin A in patients receiving renal allografts from cadaver donors. Lancet 1978; 2:1323.

161. Calne RY, Rolles K, White DJG, et al. Cyclosporin A initially as the only immunosuppressant in 34 recipients of cadaveric organs: 32 kidneys, 2 pancreases, and 2 livers. Lancet 1979; 2:1033.

162. Starzl TE, Weil R III, Iwatsuki S, et al. The use of cyclosporin A and prednisone in cadaver kidney transplantation. Surg Gynecol Obstet 1980; 151:17.

163. Starzl TE, Klintmalm GBG, Porter KA, et al. Liver transplantation with use of cyclosporin A and prednisone. N Engl J Med 1981; 305:266.

164. Shaw BW Jr., Martin DJ, Marquez JM, et al. The advantages of venous bypass during orthotopic transplantation of the liver. Semin Liver Dis 1985; 5:344.

165. Griffith BP, Shaw BW Jr., Hardesty RL, et al. Veno-venous bypass without systemic anticoagulation for transplantation of the human liver. Surg Gynecol Obstet 1985; 160:270.

166. Kino T, Hatanaka H, Miyata S, et al. FK 506, a novel immunosuppressant isolated from Streptomyces. II. Immunosuppressive effect of FK 506 in vitro. J Antibiot (Tokyo) 1987; 40:1256.

167. Ochiai T, Nakajima K, Nagata M, et al. Effect of a new immunosuppressive agent, FK 506, on heterotopic allotransplantation in the rat. Transplant Proc 1987; 19:1284.

168. Starzl TE, Makowka L, Todo S, Eds. FK 506, A potential breakthrough in immunosuppression. Transplant Proc 1987; 19(Suppl 6):1.

169. Starzl TE, Todo S, Fung J, et al. FK 506 for human liver, kidney and pancreas transplantation. Lancet 1989; 2:1000.

170. Tzakis AG, Fung JJ, Todo S, et al. Use of FK 506 in pediatric patients. Transplant Proc 1991; 23:924.

171. Goulet O, Revillon Y, Jan D, et al. Small-bowel transplantation in children. Transplant Proc 1990; 22:2499.

172. Deltz E, Schroeder P, Gebhardt H, et al. Successful clinical small bowel transplantation: Report of a case. Clin Transplant 1989; 3:89.

173. Woodruff MFA, Woodruff HG. The transplantation of normal tissue: With special reference to auto- and homotransplants of thyroid and spleen in the anterior chamber of the eye, and subcutaneously in guinea pigs. Phil Trans 1950; 234:559.

174. Starzl TE, Demetris AJ, Van Thiel D. Medical progress: liver transplantation. N Engl J Med (Part I) 1989; 321:1014.

CURRICULUM VITAE

Thomas Earl Starzl

PERSONAL

Born:	March 11, 1926; Le Mars, Iowa
Marital Status:	Married to Joy Denise (nee Conger); 3 Children

EDUCATION

1950	Northwestern University, Chicago, IL, Ph.D.
1952	Northwestern University, Chicago, IL, M.D.

BOARD CERTIFICATION

1958	General Surgery
1959	Thoracic Surgery

POSITIONS

1958	Instructor in Surgery, Northwestern University, Chicago, IL
1959	Associate in Surgery, Northwestern University, Chicago, IL
1961	Assistant Professor in Surgery, Northwestern University
1962	Associate Professor in Surgery, University of Colorado
1964-80	Professor in Surgery, University of Colorado
1972-80	Chairman of Surgery, University of Colorado
1981-	Professor of Surgery, University of Pittsburgh
Present	Presbyterian University Hospital of Pittsburgh, Children's Hospital of Pittsburgh and Veterans Administration Hospital of Pittsburgh (Oakland)

PROFESSIONAL SOCIETIES

Total: 52

International Transplantation Society

1970	Vice President
1990	President

American Society of Transplant Surgeons

1975	Founding President

Transplant Recipients International Organization

1987	Founding President
1987	Permanent Honorary Chairman

AWARDS

1950	Alpha Omega Alpha
1952	Student Borden Award
1959	Markle Scholarship
1965	Alumni Achievement Award, Westminster College
1965	Prix Société International de Chirurgie

1967	Colorado Man of the Year Award
1968	William S. Middleton Award, Outstanding Research in Veterans Administration System
1969	Merit Award, Northwestern University
1970	Eppinger Prize, Freiburg
1970	Deutsche Gesellschaft fur Chirurgie, Munich
1971	American Academy of Arts and Sciences
1971	Award, Council Creative Research (highest award, University of Colorado)
1974	Brookdale Award (highest award of AMA to person under 50 years)
1975	Josiah Macy Scholar
1976	Robert L. Stearns Award (highest award of Colorado Alumni Association)
1977	Centennial Medallion of University of Colorado
1978	David M. Hume Memorial Award (highest Award of the National Kidney Disease Foundation)
1981	Pittsburgh Man of the Year
1982	Sheen Award, American College of Surgeons
1983	Golden Plate Award, American Academy of Achievement
1983	First Uremia Award, The International Uremia Society
1984	Pittsburgh Man of Year Award by Pittsburgh Academy of Medicine
1984	Honorary Fellow royal College of Surgeons, England (Hon. F.R.C.S., Eng.)
1984	"Membre d'Honneur Etranger" de La Société de Chirurgie de Lyon ("Foreign Honorary Member" of the Surgery Society of Lyon)
1985	Annual Lecturer, Fondazione Giovanni Lorenzini, Italy
1985	Pennsylvania Medical Society Distinguished Service Award
1986	Alumni Medal Northwestern University
1986	Pittsburgh Man of the Year
1986	Biannual Prize of Italiane Hepatology Society presented at Chiaciano, Italy
1986	Distinguished Service Professor of Health Sciences of University of Pittsburgh
1986	Key to the City of Milan
1987	Key to the City of Venice
1987	Jewish National Fund, "Friend of Israel" Award
1987	Ireland (Hon. F.R.C.S., I.)
1987	Honoree International Organ Transplantation Forum
1989	Bigelow Medal, Boston Surgical Society
1989	City of Medicine Award, Durham, NC
1990	Medallion for Scientific Achievement, American Surgical Association
1990	Pittsburgh Surgical Society Annual Award

1990	Glasgow, Physicians and Surgeons (Hon. F.R.C.S., G)
1991	Honorary Member Asian Surgical Association
1991	American Liver Foundation Distinguished Service Award
1991	William Beaumont Prize in Gastroenterology, New Orleans
1991	Recipient Hugh R. Butt Award, American Gastroenterological Association
1991	American Association for the Study of Liver Disease Distinguished Service Award
1991	Designated "Thomas E. Starzl Surgical Ward," Denver VA Hospital
1991	Fondazione Basile Prize World Association of Hepato-Pancreato-Biliary Surgery, Italy
1991	Elu associé étranger (Foreign Member) Academie Nationale De Medecine (French Academy of Medicine), Paris, France

HONORARY DOCTORATES

1968	Westminster College, D.Sc.
1970	New York Medical College, D.Sc.
1971	University of Wyoming, L.LD
1974	Westmar College, D.Sc.
1981	Medical College of Wisconsin, D.Sc.
1982	Northwestern University, D.Sc.
1985	University of Louvain, Belgium, D.Med.
1985	Bucknell University, D.Sc.
1985	Muhlenberg College, D.Sc.
1988	University of Rennes, D.Med.
1988	Mt. Sinai School of Medicine, D.Sc.
1988	La Roche College, D.H.L.
1988	Bologna, D.Med.

EDITORIAL BOARDS AND EDITORSHIPS

Total: 26

PUBLICATIONS

Total: Scientific Articles 1,400

Books: Full Books 4
Chapters 163

Presentations at Major Meetings 880

TRANSPLANTATION: A PERSONAL RECOLLECTION

Sir Michael Woodruff

Address: 506 Lanark Road
Juniper Green
Edinburgh EH14 5DH
Scotland, UK

Sir Michael Woodruff

1969

ca. 1946

1986

TRANSPLANTATION: A PERSONAL RECOLLECTION

Sir Michael Woodruff

Edinburgh, Scotland
United Kingdom

My interest in transplantation began soon after Singapore fell to the Japanese in 1942 and I became a prisoner of war. We had managed to salvage a goodly number of books from various libraries, load them with other possessions on abandoned trucks, and manhandle these - since we had no fuel - to Changi, where we were to be incarcerated. Among the books was Rodney Maingot's *Postgraduate Surgery* (1) and, thumbing through this one day, I read to my surprise that skin grafts transplanted from one person to another (for which I shall use the current term allograft) did not, as a rule, survive permanently. Hitherto the only grafts I had learned about apart from blood transfusion were autografts of skin and bone, and allografts of cornea, and I had assumed, insofar as I thought about the matter at all, that one used autografts simply as a matter of convenience, except when this was manifestly impossible, as in the case of cornea. My father was a bacteriologist with a particular interest in immunology, and had conveyed to me his interest in the ability of man and other mammals to distinguish between proteins as similar as hen egg albumin and duck egg albumin, but how could anyone distinguish between his own skin and that of someone else yet fail to make a similar distinction in the case of a cornea? I resolved that if, unlikely as it seemed, I survived the war, I would investigate the matter.

When the war did end and I returned to Australia, I learned of the work of Gibson and Medawar (2) with allografts of human skin and of Medawar's subsequent experiments in rabbits (3) that established the immunological nature of allograft rejection. Soon afterwards I moved to England, to a post in the Department of Surgery at the University of Sheffield and as soon as possible made contact with Medawar, who was then head of the Department of Zoology in Birmingham.

At that time, to start working on transplantation was like joining a small select club. The members of the club included Peter Medawar and Peter Gorer in England, and John Converse, David Hume, and Harry S. N. Greene in the United States. Keeping up with the literature was not the problem that it is now, but one had to look critically at earlier work, and I was particularly interested to read Leo Loeb's *The Biological Basis of Individuality* (4) and J. B. Murphy's *The Lymphocyte in Resistance to Tissue Grafting, Malignant Disease, and Tuberculous Infection* (5).

I was impressed by H. S. N. Greene's work on the behavior of allografts in privileged sites, including the anterior chamber of the eye, and in collaboration with my wife, embarked on a study of grafts of thyroid tissue in the anterior chamber in guinea pigs. This work formed the basis of our first paper on transplantation, and it seemed to augur well for the future when this was accepted for publication by the Royal Society (6). We found in thyroidectomized recipients that grafts in the eye became vascularized from the iris and survived indefinitely, whereas grafts transplanted subcutaneously were invariably rejected. Grafts that became vascularized and survived for some months in the anterior chamber appeared to undergo some kind of adaptive change in consequence of which they could quite often be retransplanted successfully to a subcutaneous site. Grafts in the anterior chamber did not survive in animals that had previously rejected a subcutaneous graft from the same donor, and from this we concluded that the state of immunity induced by a subcutaneous graft extends to the anterior chamber; it seemed, therefore, that if an anterior chamber graft induces immunity, it does so sufficiently slowly for the graft to become adapted before this happens.

If allograft rejection was an immunological phenomenon, what antigens were involved? As long ago as 1924 there was good evidence that compatibility in respect to the ABO red cell antigens was not sufficient to ensure survival of skin allografts. A quarter of a century later many other red cell antigens had been discovered, and I wondered whether compatibility, in respect of all of these, might suffice. The opportunity to investigate this came in 1952 when I was in the Department of Surgery at the University of Aberdeen, and found that 100 registered blood donors had recently been typed in respect to all the red cell antigens then known. Among these donors were two who had precisely the same array of antigens (O; cde/cde; MN; S-ve; Kell-ve; Le (a)-ve, (b)+ve; Lu-ve; Duffy+ve). The people concerned, one of whom happened to be a physician, generously agreed to my request that after tests to exclude the possibility of transmissible disease, they would allow me to interchange small whole-thickness skin grafts between them. This was done, and control autografts were set up at the same time. All the grafts took, but the allografts were completely rejected within three to four weeks whereas the autografts survived permanently (7), and from this we concluded that there must be other antigens involved in allograft rejection. In discussing these findings we suggested that "methods of typing based on the antigenic properties of leukocytes, could they be developed, might be of value in guiding the choice of a donor for homografts of skin." It was not long before this prediction was confirmed (8), though, sadly, not by us.

Soon after our move to Aberdeen, Macfarlane Burnet and his wife came to stay with us for a few days, and we talked at length about the prediction he and Frank Fenner had put forward (9) that an animal would become tolerant of antigens it encountered during early embryonic life. We set out to see if this held good for the antigens concerned in allograft rejection by grafting a minute piece of skin from a rat of a different strain to rat fetuses in utero and challenging the survivors with donor-strain skin when they were a few weeks old. None of them showed any evidence of tolerance, and it was chastening to learn later of the experiments of Billingham, Brent, and Medawar (10) in which they succeeded in inducing tolerance by injecting fetal mice with allogeneic lymphoid cells. This was clearly a better way to proceed, though they were lucky in their choice of strains because, at the time, graft-versus-host disease was unknown and they might easily have chosen a combination of strains which resulted in the death of all the recipient animals.

In 1953 I was appointed to the Chair of Surgery in the Medical School of the University of Otago, in Dunedin, New Zealand. There was, at the time, no plastic surgeon in Dunedin, and it fell to me to set up a unit for the treatment of severe burns, which were surprisingly common, especially in children. We found that allografts of partial thickness skin that had been frozen in 15 percent glycerol and stored at -79°C, were very useful as temporary cover, and usually survived for two to three weeks. By this time the patient's general condition had improved greatly, and the allografts could be replaced by autografts, which virtually always took well (11). Of course it would be even better if the allografts could be made to survive permanently, and after showing in the laboratory that newborn rats could be made tolerant of allogeneic skin (12) and other tissues (13) by injection of donor-strain lymphoid cells, we wondered whether the same might be true of human infants. I discussed the matter in a lecture I gave in the Medical School and privately with various colleagues, and at the time it was generally agreed that to attempt this would not involve any danger if the infant was male, though the possibility of causing Rhesus sensitization would have to be excluded if it was female. I was still pondering the question of whether the procedure would be ethically justifiable when a technician who had heard my lecture asked me if I would attempt to induce tolerance to his tissues in his newborn son. After full discussion with both parents I agreed, and proceeded to inject blood leukocytes from the father intramuscularly to the baby. This had no discernible deleterious effect so, six months later, I transplanted a very small piece of skin from the father to the baby under local anesthesia. I repeated the procedure in another newborn boy, again after full discussion with both parents (14). In each case the graft took but was subsequently slowly rejected. We were disappointed at the time, though very relieved later when it was discovered that allogeneic leukocytes injected to newborn rats and mice can react against the recipient and cause serious graft-versus-host disease. There would seem to be two reasons, either of which is sufficient, to account for the fact that neither of these infants came to any harm: firstly, we had injected the leukocytes intramuscularly, not intravenously; and, secondly, the human infant at birth is immunologically more mature than the newborn rat. It was nevertheless a salutary warning that, however thoroughly one tries to assess the risks of a new procedure in humans, one can never completely exclude risks due to phenomena which, at the time, have not been discovered. It is, in my opinion, incumbent on all who undertake research in man to discuss this uncertainty with the people concerned.

I wondered whether or not tolerance would be abolished if all the antigen used to induce tolerance was removed or destroyed. It seemed just conceivable that, even though our minute skin grafts to fetal rats had not induced tolerance, a much larger graft to a newborn rat might do so, and, if it did, it would be interesting to see if tolerance was lost when this graft was removed. To my great delight, in 1956, Peter Medawar accepted an invitation to come to the University of Otago as Visiting Professor, and I suggested to him that we might set up some collaborative experiments to test this. He agreed and, as a result of careful planning by letter, we managed to do this during the course of his visit. I already knew that he had a penetrating intellect, but I did not know until he came to Dunedin what a very skillful pair of hands he possessed. The results of these experiments were not as clear-cut as we would have liked, but a few of our skin graft recipients developed demonstrable tolerance and accepted a second graft of donor-strain skin at the age of eight weeks, and removal of the initial graft four weeks after birth reduced, though it did not abolish, the probability of this happening (15). At the time we were disappointed but today it is perhaps surprising that we achieved even this limited success.

Shortly before Medawar arrived in New Zealand I had noticed that some of the animals in which we had tried to induce tolerance died for no apparent reason. When I told him about this he said that it was almost certainly due to graft-versus-host disease, which had recently been discovered by Billingham and Brent (16), though their work had not as yet been published.

As already mentioned, our experiments with grafts in the anterior chamber of the eye suggested that if, for some reason, an allograft survived beyond a certain critical period (17), it ceased to be susceptible to destruction by the immunological reaction of the host. We called this "graft adaption." Later we used the same term in relation to the fact that in some animals in which we had tried to induce tolerance, an initial skin graft survived permanently, whereas a second graft from the same donor strain did not, but we were careful to point out that in each case it was used in a purely descriptive sense and that the underlying mechanisms might well be different (18).

As a sequel to our work on the behavior of allografts in immunologically privileged sites, I became interested in trying to create an artificially privileged site by interposing a membrane permeable to fluid but not to cells between a graft and the tissue of the host. This procedure was pioneered by Glen Algire, who enclosed grafts of various tissues in what he termed diffusion chambers (19); we simply interposed a piece of membrane, similar to the membrane he had used, between a split skin graft and a bed prepared by removing host skin down to the level of the subcutaneous muscle (20) that is widespread in many animal species, though represented in man only by the platysma muscle in the neck and the dartos muscle in the scrotum. Later, I decided to study what seemed to be the best of all immunologically privileged sites, namely the gravid mammalian uterus, in which the fetus receives fluid and various soluble substances from its mother via the placenta, but normally is not exposed to circulating maternal cells. Studies in rats of the behavior of pieces of fetal tissue transplanted to extra-uterine sites in the mother led me to conclude that the anatomical separation of fetus and host by the placenta is sufficient, and also necessary, to safeguard the mammalian fetus from the immunological hazards of pregnancy, though various other factors may play a subsidiary role (21).

In 1957 I was appointed to the Chair of Surgical Science (later renamed the University Chair of Surgery) at the University of Edinburgh and Surgeon to the Edinburgh Royal Infirmary. It was easier then than it is now to obtain money for research, and the Medical Research Council agreed to establish a research group on transplantation in my department, under my direction. The first person appointed was Dr. Norman Anderson, who had been house surgeon to Thomas Gibson, the plastic surgeon in Glasgow who had collaborated with Peter Medawar in the clinical phase of the work that established the immunological nature of allograft rejection. Soon afterwards, Drs. Donald Michie and James Howard joined the group.

Our research in transplantation was pursued in the laboratory and clinically simultaneously, but for purposes of description it will be convenient to consider the experimental work first. This was concerned mainly with a) the development and characterization of antilymphocytic serum (ALS) and globulin (ALG) as immunosuppressive agents, and b) specific immunological tolerance of allografts and related phenomena.

My first attempt to develop an antilymphocytic serum with immunosuppressive properties had been made in collaboration with my wife when we were in Aberdeen, but we did not have much success. I returned to the problem in Edinburgh with the help of Norman Anderson, and this time we succeeded. As "antigen," we used lymphocytes obtained by cannulating the thoracic duct of the rat and raised a serum in rabbits that prolonged the survival of skin allografts from hooded to Wistar rats from the eight days we observed in untreated recipients to 75 days; and when the recipients were also subjected to prolonged drainage of lymph from the thoracic duct, allografts often survived permanently (22). Later we raised ALS against dog thoracic lymphocytes in horses and showed that this could greatly prolong the survival of whole kidney allografts (23). It was not long before others began to be interested in ALS, among them Peter Medawar in London, and Paul Russell and Tom Starzl in the United States.

It seemed important to develop in vitro assays that would reflect the antilymphocytic effect of ALS in vivo and also to elucidate its mode of action. For this we needed someone with expertise in immunochemistry and were fortunate to find just the person we needed when Keith James joined our group. Our work generated many papers, but most of it is summarized in two reviews (24,25). We also wanted to raise ALS for clinical use, and because of the quantity required we obtained six horses to provide this. The licensing authority for animal experiments in the United Kingdom insisted that there should be a qualified veterinarian on our team for all procedures in which horses were used, even though this involved only giving injections and taking blood. Up to this time a colleague from the Veterinary School, Dr. John Watt, had kindly collaborated with us, but when we decided to step up production we needed someone who could devote more time to the project, and invited another veterinarian, Dr. Roger Dalton, to join the group.

Our work on tolerance included an investigation of the nature of tolerance based on chimera analysis (26), the induction of tolerance to heterografts of rat skin in newborn mice (27), and the induction of tolerance to allografts in adult mice by sublethal irradiation and injection of donor-strain spleen cells in high dosage (28). As long ago as 1959 I had raised the question of whether there were such things as tolerant cells (29). Peter Medawar agreed at the time that this was an important question but thought, as I then did, that it would be easy to answer; it proved, however, much more difficult than we had expected. Chimera analysis (26) established that tolerance was a property not only of whole animals but also of aggregations of lymphoid cells but left open the possibility that it was due to selective clonal elimination, in which case what seemed to be a tolerant cell might simply be a cell that was not there. Today, our understanding of tolerance is deeper, and this loophole has been filled.

We were also interested in tolerance-like phenomena: in particular, immunological enhancement, dependent on the presence of enhancing antibody, and the puzzling "blood transfusion effect," first described by Opelz and Terasaki (30). To investigate the transfusion effect experimentally, we studied the effect of pretreatment with whole blood, blood serum, and spleen cells on the survival of heart allografts in rats (31,32). Possible explanations of the phenomenon are discussed in a later paper written in collaboration with J. J. van Rood (33).

When I arrived in Edinburgh, clinical transplantation of bone marrow and of the kidney were under investigation in the United States and France, and it seemed time for us to move cautiously into this field. Inspired by the work of Joseph Ferrebee and Donnell Thomas at Cooperstown - better known perhaps as the place where baseball began - and by others on both sides of the Atlantic, we became interested in the possibility of using autologous bone marrow and allogeneic fetal liver, in association with wide-field irradiation or chemotherapy, in patients with advanced cancer (34). Later, after many experiments in animals, we extended this by using autologous or allogeneic spleen cells. With allogeneic spleen cells there was the danger of severe graft-versus-host disease, but we tried to develop a regime which provided a significant graft-versus-tumor effect while keeping the damage to normal host tissue caused by the graft-versus-host effect down to an acceptable level.

To have any chance of getting kidney transplantation off the ground in conservative Edinburgh, we would have to convince our nephrological colleagues that it was worthwhile, and this meant that our first case had to be a resounding success. At the time, the only way of ensuring this was

Michael Woodruff leaving home in Edinburgh in about 1960

Michael Woodruff (right), his wife Hazel, and his oldest son Keith in Edinburgh, 1964 to wait until we had a patient in desperate need of a transplant who was fortunate enough to have a healthy identical twin who was willing to donate a kidney. In these circumstances the transplant would be expected to survive indefinitely without immunosuppression, and the truth of this surmise had been demonstrated for the first time in 1956 by Murray and his colleagues in Boston (35).

Our wait ended when a 45-year-old man with advanced renal failure attributed to pyelonephritis was asked - initially, it is said, by a candidate in the examination for Membership of the Royal College of Physicians of Edinburgh who had heard a lecture of mine on transplantation - if he had a twin, and replied that he had a twin brother. The appearance of the twins, allowing for the fact that one was in advanced renal failure and the other in good health, and many investigations, including fingerprinting, pointed strongly to the conclusion that they were homozygous, and this was confirmed when skin grafts exchanged between them behaved indistinguishably from autografts. A garbled account in the press stated that the twins' fingerprints were indistinguishable, and this greatly alarmed the police, who envisaged the possibility of suspected criminals claiming that fingerprints which were supposed to be theirs must be those of a long lost twin. They were greatly relieved when I told them that, while the prints showed areas of great similarity, there were other areas where one print was a mirror image of the other and others again that were markedly different.

An attempt to perform retrograde aortography on the donor failed owing to atherosclerosis of his iliac vessels, and it was felt at the time that it was not justifiable to subject him to translumbar aortography. I had decided that if, as proved to be the case, there were two renal arteries on the donor kidney, I would anastomose one to the anterior division and the other to the posterior division of the recipient's internal iliac artery, but I was unable to do so because this vessel was completely occluded by atheroma. A new plan had to be devised in a hurry, but fortunately this was successful.

I had an extra assistant for the operation on the donor in the person of a distinguished urological colleague, whom I will call Peter, though that was not his real name, who had persuaded me, against my better judgment, to allow him to scrub. I left my patient for a few minutes to inspect the donor kidney that my colleague, James Ross, had exposed in the adjacent operating theater, and in my absence Peter took it upon himself to feel round in the pelvis. When I returned he was looking very pale. "Michael," he said, "he's got a carcinoma of the bladder." I had cystoscoped the patient myself and could not believe this. "Are you sure," I replied, "that what you felt is not just the bag of the Foley catheter?" as indeed it was. Poor Peter. My only comment is that even experienced surgeons can make bizarre mistakes, especially when they are not on their home ground.

The donor and recipient recovered quickly from their operations, and the transplant developed normal renal function. They remained well for six years when the donor collapsed and died in the street. At autopsy, the cause of death was clearly acute myocardial infarction due to coronary artery thrombosis, but he also had a small carcinoma of the stomach. Some weeks later the recipient came to see me complaining of loss of weight, pallor, and epigastric discomfort. A barium meal showed a large gastric carcinoma, and at laparotomy there were numerous metastases in the liver. He died soon afterwards. He had not received any immunosuppressive therapy, and one is forced to conclude that both twins must have had an inherited disposition to gastric cancer.

Our second renal transplant was from a brother to his sister, and the recipient was given whole body irradiation to prevent rejection. The transplant developed good function, but she died four weeks after operation from septicemia due to severe bone marrow failure with almost total absence of polymorphonuclear leukocytes in the peripheral blood. We had taken great care to minimize the risk of infection from any external source but had not been able to prevent invasion of the blood stream by the patient's own intestinal organisms.

Our third patient, who received a kidney from his father in July 1962 when he was 11 years old, is still alive. Three months before I first saw him, Dr. Joseph Murray had visited me in Edinburgh and had told me of the exciting work in Boston on immunosuppressive drugs, in which Roy Calne had played a leading role. Subsequently, Joe had been my guest at a meeting of the Association of Surgeons of Britain and Ireland in Swansea. It was raining when we got to the meeting, and when I checked my coat I was given a tag bearing the number 322. Joe looked at this in amazement. "That's the number of our latest drug," he said, "Burroughs Wellcome 322, made by George Hitchings and Trudy Elion. This must be a good omen; I will send you some." He was as good as his word, and a good omen it proved to be.

Though we did not know it until several years later when the donor and host were typed for HLA by Dr. van Rood, the boy's father and mother happened to have an HLA haplotype in common, and as he had inherited this common haplotype from his mother, he was HLA-identical with his father, who provided the transplant. For immunosuppression we used only azathioprine; a year after transplantation the dose was reduced to only 10 mg/day and after five years was withdrawn completely. To our surprise this was followed by an acute rejection crisis, and, despite prompt treatment with prednisone and azathioprine, it took more than a year to get his renal function back to normal. This was a salutary demonstration that the so-called minor histocompatibility antigens may, in their totality, be of quite major importance. Thereafter, function was well maintained until some 25 years after the original operation, when it began to decline and the patient was given a second transplant by my successor, Professor G. D. Chisholm.

Our first patient to receive a kidney from a cadaver was a man aged 54 who was referred to me in 1965 by a urologist because he had had one kidney removed three years previously on account of a carcinoma and now had a similar tumor in his remaining kidney. The kidney was still functioning, so, to avoid putting him on dialysis, I performed the transplantation first and removed the patient's own kidney a few days later. The tumor was enormous, and at operation there was neoplastic tissue growing along the renal vein as far as the vena cava. It seemed unlikely that the patient would survive very long, but he remained well for five years, during which time he played golf, summer and winter, on the Old Course at St. Andrews. His own account of his golfing exploits was so remarkable that my Senior Registrar, Michael Middleton, who was a good golfer, challenged him to a game on the championship course at Muirfield. The movie that we took of the contest shows a sunburned athletic figure and his rather pallid opponent, the athletic figure being the patient. Though not quite as good as he had claimed, he was a competent golfer by any standards and, I suspect, unique at the time among renal transplant recipients. Five years later he began to feel poorly, though his renal function was normal. His chest x-ray was accepted as normal, though by hindsight one can just discern some scattered metastases. A month later there were obvious metastases in both lungs, and soon after this he died with metastases widely disseminated throughout the body. We could not find any reason to account for the fact that the tumor had remained so quiescent for so long and then suddenly burst into furious activity.

In all, between 1960 and the end of 1974, 127 patients with end-stage renal failure were treated by renal transplantation in Edinburgh. In two cases the donor was an identical twin, in 22 the donor was a parent or a nontwin sibling, and in the rest a cadaver kidney was used. These cases were reviewed just before I retired from surgery (36). A considerable number of them were operated on by my colleague, Bernard Nolan.

The operative technique we used was similar to that described by Murray except as regards anastomosis of the ureter of the transplant to the patient's bladder. For this, in nearly all of our patients, we used a very simple procedure that we described in detail when we reported our first 35 cases in 1969 (37). I felt honored when Tom Starzl and his colleagues rediscovered this technique some twenty years later (38).

For immunosuppression we used azathioprine and steroids in the way current at the time. Eleven patients also received ALG, and the value of this is discussed below.

I also became involved in one case of transplantation of a lung (39), though the operation was performed by my colleague, Mr. Andrew Logan. The patient, a boy aged 15, was admitted to the Poisons Unit at the Edinburgh Royal Infirmary in September 1968, the day after he had swallowed a mouthful of a weedkiller called paraquat (Gramoxone W, 1,1'dimethyl-4,4'dipyridilium) from a bottle labelled "Kola" at his home in Stornaway. Despite treatment by forced osmotic diuresis, he gradually developed severe respiratory distress, and six days after ingestion of the poison, the left lung, which showed more marked radiological changes than the right, was removed and replaced by a lung from an 18-year-old girl who had died from severe gastrointestinal hemorrhage following poisoning with ferrous sulphate and paracetamol. Immunosuppressive therapy with azathioprine and prednisone followed the pattern we were then using in renal transplant recipients. The pathological changes in the patient's own lung steadily progressed. The transplant functioned well for a week, after which the patient developed respiratory distress and cyanosis despite assisted respiration and died 13 days after the operation. At autopsy the pathological changes in the transplant were similar to those in the patient's own lung and were thought to be due to residual paraquat in the circulation rather than rejection. Today treatment might have taken the form of immediate hemodialysis to eliminate the poison as quickly as possible, followed if necessary by transplantation of the heart and both lungs, but one can only speculate as to what the result might have been.

The ideal to aim at in organ transplantation, or indeed any other operation, is to restore to the patient the life-expectancy, as regards both quality of life and its duration, of a normal person of the same age and sex. In the case of renal transplantation great progress has been made, and continues to be made, towards this goal. One illustration of this is the number of women who have undergone successful pregnancy after receiving a renal transplant, including two of our patients. Another of our patients, it may be added, successfully fathered a healthy infant after he received his transplant. We are, however, still limited by the lack of a sufficient number of suitable kidneys for transplantation and by the problem of rejection.

As regards prevention of rejection, HLA-matching has helped considerably, but it is still true, as I remarked many years ago, that "there seems to be little hope of being able to rely on matching alone without any form of immunosuppression, since even if tests of a sufficiently high resolving power could be devised, the chance of finding a completely compatible donor for a given patient (in the absence of an identical twin) would be so small as to be negligible" (40).

Clinical trial of ALG in Edinburgh was rather disappointing (36) but suggested that it might be useful for treating episodes of rejection, and that, when ALG was given in conjunction with azathioprine and prednisone for routine immunosuppression, it might be possible to reduce the dose of prednisone appreciably. The Medical Research Council agreed to my proposal that a multicenter trial should be set up to investigate the matter further, using ALG prepared by the Wellcome Foundation. Unfortunately, the material they produced was certainly no more immunosuppressive, and decidedly more toxic, than the material we prepared, and the trial was abandoned, though ALG continued to be used for quite a long time on both sides of the Atlantic, especially in patients receiving heart transplants. Interest in ALG waned still further with the development of cyclosporine and other new immunosuppressive drugs but has been rekindled by the development of monoclonal antibodies specific for various categories of T cells, which may well play an important role in further attempts to induce specific tolerance to donor tissue in prospective transplant recipients. To achieve this safely would be to win a pearl of great price, or, if you prefer, a therapeutic jackpot, but this goal has proved very elusive. That is one of the reasons why, some years before I retired from surgery, I decided to expand my area of research to include the related topic of tumor immunology. Many tumors express antigens not expressed by the normal tissues of the host, and I argued, perhaps rather naively, that, if a new drug failed to suppress immunity to allografts, it would be worth looking to see if it had the opposite effect and actually potentiated the immune reaction, in which case it might find a place in the treatment of cancer. However, as a former Prime Minister of Australia, Mr. Malcolm Fraser, once remarked, "Life wasn't meant to be easy," and we found that the heterogeneous nature of tumor cell populations and their remarkable capacity to diversify, makes them very elusive targets for immunotherapeutic, or indeed chemotherapeutic, attack (41).

But that, as they say, is another story.

REFERENCES

1. Maingot R. Postgraduate Surgery. London, 1936.
2. Gibson T, Medawar PB. The fate of skin homografts in man. J Anat 1943; 77:299.
3. Medawar PB. The behaviour and fate of skin autografts and skin homografts in rabbits. J Anat 1944; 78:176; J Anat 1945; 79:157.
4. Loeb L. The Biological Basis of Individuality. Springfield, Thomas, 1945.
5. Murphy JB. The lymphocyte in resistance to tissue grafting, malignant disease, and tuberculous infection. Monographs of the Rockefeller Institute for Medical Research 1926; 21.
6. Woodruff MFA, Woodruff HG. The transplantation of normal tissues: with special reference to auto- and homotransplants of thyroid and spleen in the anterior chamber of the eye, and subcutaneously, in guinea pigs. Phil Trans B 1950; 234:559.
7. Woodruff MFA, Allan TM. Blood groups and the homograft problem. Br J Plast Surg 1953; 5:238.
8. History of HLA: Ten Recollections. In: Terasaki PI, Ed. Los Angeles, UCLA Tissue Typing Laboratory, 1990.
9. Burnet FM, Fenner F. The Production of Antibodies. 2nd ed. Melbourne, MacMillan, 1949.

10. Billingham RE, Brent L, Medawar PB. Actively acquired tolerance of foreign cells. Nature 1953; 172:603.

11. Woodruff MFA. Transplantation of tissues and organs. In: Taylor S, Ed. Recent Advances in Surgery. Churchill, London, 1959.

12. Woodruff MFA, Simpson LO. Induction of tolerance to skin homografts in rats by injection of cells from the prospective donor soon after birth. Br J Exp Pathol 1955; 36:494.

13. Woodruff MFA, Sparrow M. Induction of tolerance to homografts of thyroid and adrenal in rats. Q J Exp Physiol 1958; 43:91.

14. Woodruff MFA. Can tolerance to homologous skin be induced in the human infant at birth? Transplant Bull 1957; 4:26.

15. Medawar PB, Woodruff MFA. The induction of tolerance by skin homografts on newborn rats. Immunology 1958; 1:27.

16. Billingham RE, Brent L. Simple method for inducing tolerance of skin homografts in mice. Transplant Bull 1957; 4:66.

17. Woodruff MFA. The "critical period" of homografts. Transplant Bull 1954; 1:221.

18. Woodruff MFA. Evidence of adaptation in homografts of normal tissue. In: Biological Problems of Grafting. Les Congrès et Colloques de l'Université de Liège 1959; 12:83.

19. Algire GH, Weaver JM, Prehn RT. Studies on tissue homotransplantation in mice, using diffusion-chamber methods. Ann NY Acad Sci 1957; 64:1009.

20. Woodruff MFA. Cellular and humoral factors in the immunity to skin homografts: experiments with a porous membrane. Ann NY Acad Sci 1957; 64:1014.

21. Woodruff MFA. Transplantation immunity and the immunological problem of pregnancy. Proc R Soc B Lond 1957; 148:68.

22. Woodruff MFA, Anderson NA. The effect of lymphocyte depletion by thoracic duct fistula and administration of antilymphocytic serum on the survival of skin homografts in rats. Ann NY Acad Sci 1964; 120:119.

23. Abaza HM, Nolan B, Watt JG, Woodruff MFA. Effect of antilymphocytic serum on the survival of renal homotransplants in dogs. Transplantation 1966; 4:618.

24. Woodruff MFA. The mode of action of antilymphocytic antibody. International Symposium of ALS. Symp Series Immunobiol Standard 1970; 16:379.

25. Woodruff MFA. Antilymphocytic serum and its mode of action. Transplant Proc 1971; 3:34.

26. Michie D, Woodruff MFA, Zeiss I. An investigation of immunological tolerance based on chimaera analysis. Immunology 1961; 4:413.

27. Reilly RW, Woodruff MFA. Induction of tolerance of rat skin in newborn mice. Transplant Bull 1961; 28:137.

28. Michie D, Woodruff MFA. Induction of specific immunological tolerance of homografts in adult mice by sublethal irradiation and injection of donor-type spleen cells in high dosage. Proc Roy Soc B Lond 1962; 156:280.

29. Woodruff MFA. Discussion to paper by N. A. Mitchison. Biological Problems of Grafting. Les Congrès et Colloques de l'Université de Liège 1959; 12:258.

30. Opelz G, Terasaki PI. Poor kidney transplant survival in patients with frozen-blood transfusions or no transfusions. Lancet 1974; i:696.

31. Jenkins AMcL, Woodruff MFA. The effect of prior administration of donor strain blood or blood constituents on the survival of cardiac allografts in rats. Transplantation 1971; 12:57.

32. Jenkins AMcL, Woodruff MFA. Specific immunosuppression of cardiac allograft rejection in rats. Transplant Proc 1973; 5:727.

33. Woodruff MFA, van Rood JJ. Possible implications of the effect of blood transfusions on allograft survival. Lancet 1983; i:1201.

34. Woodruff MFA. The surgery of replacement. J R Coll Surg Edinb 1957; 3:19.

35. Merrill JP, Murray JE, Harrison JH, et al. Successful homotransplantation of human kidney between identical twins. JAMA 1956; 160:277.

36. Woodruff MFA, Nolan B, Anderton JL, et al. Long survival after renal transplantation in man. Br J Surg 1976; 63:85.

37. Woodruff MFA, Nolan B, Robson JS, et al. Renal transplantation in man. Experience of 35 cases. Lancet 1969; i:6.

38. Starzl TE, Shapiro R, Tzakis A, et al. A new technique of extravesical ureteroneocystectomy for renal transplantation. Transplant Proc 1989; 21:3856.

39. Matthew H, Logan L, Woodruff MFA, et al. Paraquat poisoning - Lung transplantation. Br Med J 1968; 3:759.

40. Woodruff MFA. Organ transplantation - retrospect and prospect. J R Coll Surg Edinb 1974; 20:96.

41. Woodruff MFA. Cellular Variation and Adaptation in Cancer: Biological Basis and Therapeutic Consequences. Oxford University Press, 1990.

CURRICULUM VITAE

Michael Woodruff

PERSONAL

Born: April 3, 1911
Marital Status: Married, 1946, Hazel Gwenyth Ashby; 2 sons, 1 daughter
Home Address: 506 Lanark Road
Juniper Green
Edinburgh EH14 5DH
Scotland, UK

EDUCATION

1932	University of Melbourne, B.E.E.
1937	University of Melbourne, M.B., B.S.
1940	University of Melbourne, M.D.
1941	University of Melbourne, M.S.
1947	F.R.C.S.
1953	F.R.A.C.S.
1957	F.R.C.S.E.
1962	University of Melbourne, D.Sc.
1975	F.A.C.S. (Honorary)
1982	F.R.C.P.E. (Honorary)
1938-40	Intern and Junior Registrar, Royal Melbourne Hospital

MILITARY SERVICE

1940-45	Captain, Australian Army Medical Corps, War Service in Malaysia, Prisoner of War for 3 1/2 years in Singapore

POSITIONS

1946-48	Tutor in Surgery, University of Sheffield
1948-52	Senior Lecturer in Surgery, University of Aberdeen
1953-57	Professor and Head of Department of Surgery, University of Otago, Dunedin, New Zealand
1957-76	Professor of Surgery (Initially Surgical Science), University of Edinburgh, and Surgeon, Edinburgh Royal Infirmary
1968-76	Honorary Director, Nuffield Transplantation Surgery Unit
1977-87	Full-time research in Medical Research Council Human Genetics Unit, Supported by grants from the MRC and the Wellcome Foundation

PROFESSIONAL SOCIETIES

Association of Surgeons of Great Britain and Ireland
Fellow, Royal Society of Edinburgh
Associaté Etranger, Academie de Chirurgie, Paris
American Surgical Society
Korrespondierenden Mittglied, Deutshe Gesellschaft für Chirurgie
Royal Society

	Fellow
1978-79	Vice President

The Transplantation Society

1972-74	President

AWARDS

1952	Hunterian Professor, Royal College of Surgeons of England
1964	Surgeon-in-Chief *pro tempore*, Peter Bent Brigham Hospital, Boston
1969	Knighthood
1969	Premio Interanazionale La Madonina, Milano
1969	Lister Medal, Royal College Surgeons, England
1974	Gold Medal, Society of Apothecaries, London
1986	Congress Dedication Award, The Transplantation Society

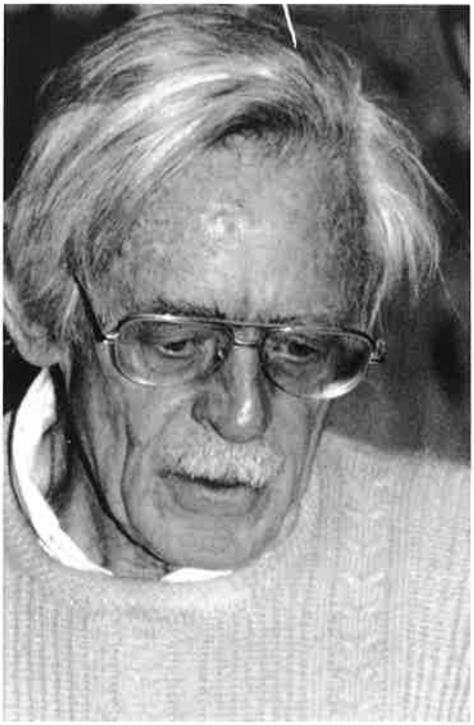
EPISODES OF THE EARLY YEARS

Ernst J. Eichwald

Address: Department of Pathology
University of Utah School of Medicine
50 North Medical Drive
Salt Lake City, Utah 84132

Ernst J. Eichwald

1961



Recent

EPISODES OF THE EARLY YEARS

Ernst J. Eichwald

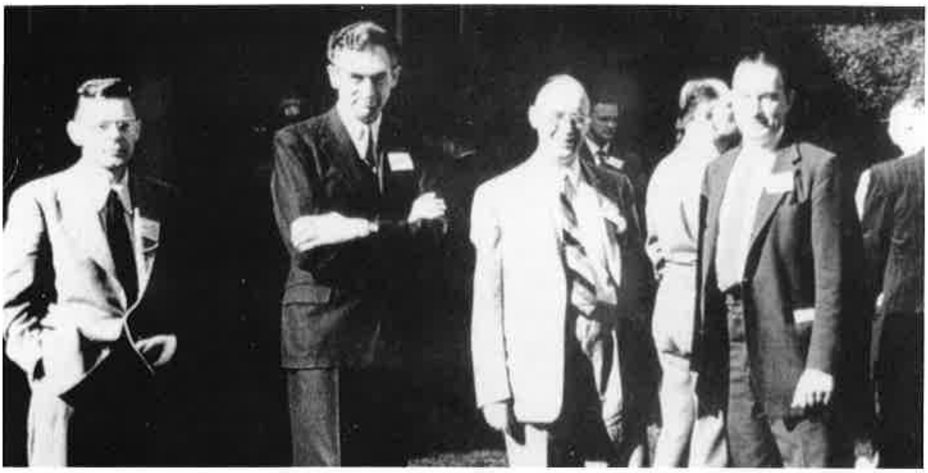
The Salt Lake Tribune, December 31, 1990, Astrology Section:
"...CANCER: a dispute could occur with a friend. Teamwork resolves many an issue today, and advisors prove helpful."

My first encounter with the world of transplantation occurred under the augury of CANCER. It was in the late 1940s, upon my return from overseas service with the United States Army, when I resumed employment as Assistant Pathologist at Boston Childrens' Hospital. I was facing seven-plus boxes of histology sections of guinea pig eyes, 100 slides per box, into which small bits of assorted childhood cancers had been inoculated in an attempt to confirm a claim by the highly intelligent, witty, and charismatic Harry S. N. Greene at Yale - namely, that growth of these tissue fragments in the anterior chamber of guinea pig eyes provided the ultimate proof of their malignant nature. These more than 700 slides were not accompanied by any paperwork regarding the time of inoculation, the clinical or pathologic diagnosis, nor the name of the transplanter. Assuredly, they represented several years of work; presumably none of the slides had been looked at before by anyone. In retrospect, it would have made no difference if any of the missing information had been available. None of the slides showed anything but granulation and scar tissue. It taught me a first research lesson: It is easier to start a project than to terminate it, particularly when the original perpetrator has departed and is followed by a series of assignees whose curiosity about the project is limited.

Detecting no cancer in any of the eyes did not keep me from pursuing the project and implanting bits of Wilms tumor or of neuroblastoma into the eyes of unhappy recipients. None of them "grew," except for a fibrosarcoma which yielded a few pink granules, histologically consistent with fibrosarcoma - or granulation tissue, for that matter.

With the support of my then chairman, the late Sidney Farber, I designed a beautifully controlled intercity experiment aimed at detecting the factors accounting for New Haven success and Boston failure. Was it a different strain of guinea pig? Was it operative technique? Was it the follow-up criteria? Armed with eight sturdy Massachusetts guinea pigs, and a slice of freshly removed neuroblastoma, I flew to New Haven having obtained expressions of concurrence and cooperation from that institution. The institution supplied its share: eight Connecticut guinea pigs, and the time and skill of their master transplanter, who on his part inoculated four of his own and four of our guinea pigs; I did the rest. Whereupon the 16 recipients were divided, leaving me, on my return home, with eight animals, two of each category, eg, two from Connecticut inoculated by me, two by my rival surgeon, etc, etc. It was a foolproof design; however, none of my eight returnees "did anything." A repeat trip south, several weeks later, ended up as a dry tap. It taught me my second lesson: even a beautifully designed experiment will lead you nowhere, unless it is supported by a persistent and shared guiding spirit.

Those were the days of seemingly unlimited NIH munificence for any study going by the name of cancer, particularly human cancer, whether it be fundamental aspects, etiology, or new diagnostic tests. They were especially interested in knowing whether claims for new diagnostic tests



Arden House, 1952
From left to right: Author, Peter Medawar, Peter Gaillard, George Gey

Peter Medawar and Jacob Furth

were true or false. Consequently, NIH was less than enthusiastic (though still munificent) when I proposed a modified approach: a) decrease the number of variables in an anterior-chamber-guinea pig eye-cancer project; and b) lower the barriers between donor and recipient, using mouse tumors and finally even mouse recipients. Their opposition to this approach, as expressed verbally by a visiting NIH envoy to my laboratory (then located in Salt Lake City), was based on the fact that they merely wanted to determine "whether Harry Greene... (expletive deleted)."

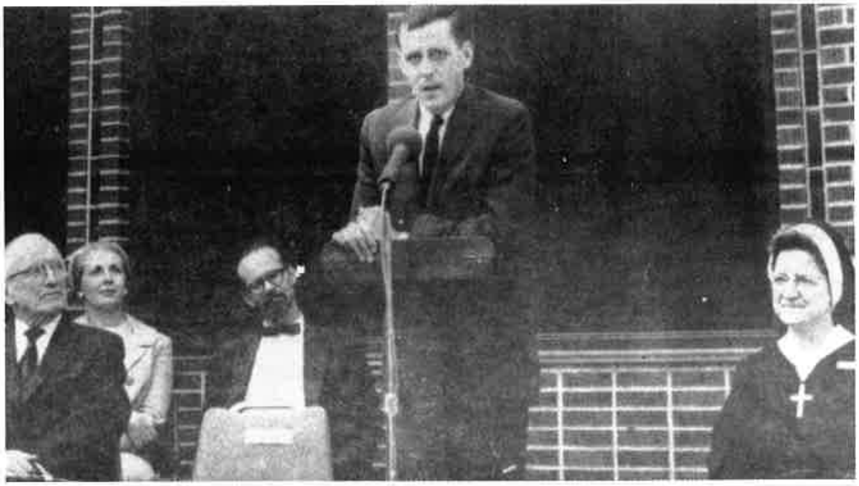
My contacts with the National Cancer Institute were helpful and appreciated; the names of Murray Sheer, "Red" Stuart, and Walt Heston recall warm memories. "Jake" Furth was helpful with (painful) criticism of a manuscript of mine on privileged transplant sites. I shall never forget my first contact with George Snell on the occasion of a Federation Meeting (?) in Madison, Wisconsin (or was it Atlantic City?). "Krebiozen" was the sensation of the day - it had been reported as the long sought-after miracle cancer cure. A semipublic meeting had been planned and controversy could be expected. NIH people and others were to confront Andrew Ivy, Professor of Physiology at the University of Illinois and the apostle of the Krebiozen crowd. The aisles were packed - not even standing room was available. I had managed to get in early and had secured a seat next to George Snell, whom I had wanted to consult regarding a pigment irregularity in one of our inbred mouse strains. We struck up a conversation, and he was just about to respond to my questions when Professor Ivy entered the auditorium. Initially, it was a courteous, straight-forward scientific debate. But gradually, and irreversibly, emotions entered, and the rising tension was unmistakable. Speakers interrupted each other, their voices raised; and the audience leaned forward in their seats. It was an extraordinary, intense drama lasting more than an hour and a half. People seemed exhausted and emotionally spent as the auditorium gradually emptied. It was then that George Snell turned to me and

1. J.M. Converse, 2. R. Prehn, 3. J. Furth, 4. H. Conway, 5. C. Little, 6. H.S.N. Greene, 7. H. Wallace-Toolan, 8. W. Heston, 9. N. Kaliss, 10. B. Rogers, 11. A.E. Casey, 12. J.Bittner, 13. R.E. Stowell

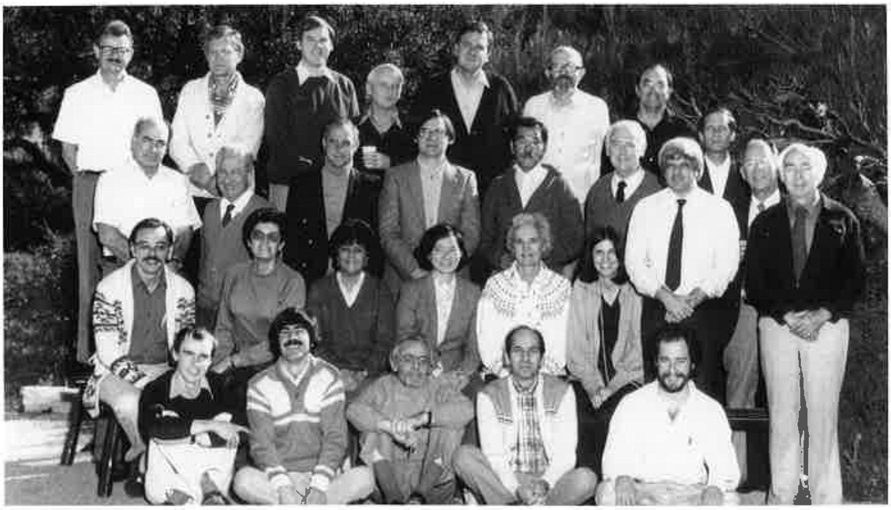
said in his slow, deliberate voice, "that skin pigmentation could be a point mutation, or possibly ..." and his voice trailed off clearly still pondering the appearance of my mouse. For a few seconds I had no idea what he was talking about, but it taught me another lesson: A great investigator must be able to concentrate on seemingly minor points.

By the early 1950s, I had begun to suspect that the behavior of transplanted cancers was only one narrow aspect of the behavior of transplanted tissues in general, although conceivably modified by specific superimposed factors. And how could the behavior of transplanted tumors be understood if there still existed questions concerning the transplantability of normal tissues? I felt tempted to change the direction of my own studies from neoplastic to normal tissues and, hopefully, to enter a field of increasing human and social need. It may have been on the flight back from the memorable meeting with George Snell that I decided to propose a meeting to the NIH aimed at bringing together transplant surgeons who worked with bone, skin, endocrine gland, or fascia, and the mouse geneticists whose most common tool was still the transplantable tumor. By that time, Peter Medawar had published his studies on transplanted rabbit skin, connected to the study of human burns incidental to the World War II blitz, and George Snell and coworkers had formulated the "Laws of Transplantation," based on transplanted tumors. A marriage of these separate fields of endeavor seemed timely. NIH, through its Study Section on "Morphology and Genetics" chaired by J. Walter Wilson from Brown University in Providence, Rhode Island, decided to sponsor such a conference, which took place at Arden House, Harriman, New York, on October 7 and 8, 1952. The proceedings were published by the *Journal of the National Cancer Institute* (vol. 14, pp. 665-767). On the face of it, this conference was a failure. Although participants shared meals and slept under the same roof, surgeons sat at one table, United States Navy officers at another, and geneticists and other biologists at a third. When vascular surgeons expanded on new suturing techniques, geneticists jotted down notes on small pads, presumably related to new experimental designs in their own laboratories but unrelated to subject matters presented by the speaker. George Snell reported in detail about breeding techniques leading to the development of coisogenic-resistant mouse lines; it was an early post-luncheon session, and the eyelids of plastic surgeons became heavier and heavier. Only Peter Medawar's charisma and oratorical skill could surmount these barriers.

The first Ciba conference, organized by Peter Medawar, took place in London, England, in 1953; it was more to the point and much better organized. The proceedings were published by the *Ciba Foundation Symposium* ("Preservation and Transplantation of Normal Tissues"). Specific tolerance induced in neonatal or even prenatal mice by injection of prospective donor-cells was at the center of interest. A.E. Casey had published extensively on the "XYZ factor," and Nat Kaliss had broadened Casey's observations. There was much musing then and later on about incomplete antibodies, low-dose tolerance, allergic death, clonal deletion, and other examples from the impressive vocabulary of theoretical immunologists. Peter Medawar was kind enough to show me his laboratory and animal rooms at Mill Hill. He wanted to show me an albino mouse with a black skin graft (or was it the other way around?) but could not locate it at that time. It was another lesson: While it initially reminded me of my New Haven episode, attempts to demonstrate a new technique or a new observation frequently fail, not because they are imaginary but because of the complexity of laboratory activities and biologic events. I greatly enjoyed postwar London, which I



Tom Starzl delivering principal address during dedication of McLaughlin Research Institute, Great Falls, Montana, 1967. McLaughlin, Dr. and Mrs. Stimpfling to speakers right.



"Errors of Sex Determination", December 8-12, 1980;
(Left to right) First row: U. Muller, G. Cunha, E. Eichwald, M. Fellous, J. Hall;
Second row: R. Gorski, N. Josso, M. New, G. Koo, P. Wright, G. Wachtel;
Third row: D. Federman, A. Jost, J. Simpson, M. Spoljar, S. Ohno, A. Gropp, S. Wachtel, U. Wolf, R. Kroc, R. Billingham;
Fourth row: A. de la Chapelle, P. Amacher, L. Pelliniemi, K. Jones, W. Van Niekerk, J. Wilson, W. Garey

had not seen since 1936 when a colleague and I attempted, late at night, to cross the British Channel from Calais, France, in a kayak, but were fished out by a British lighthouse keeper near Ramsgate.

At that time transplantation conferences were becoming fashionable. The New York Academy of Sciences began its series, spurred on by the dynamic energy of Blair Rogers, and the proceedings, widely read and distributed, contained a wealth of information. At a later transplant congress, Peter Medawar referred to these seemingly unending yellow grey volumes piling up on our bedside tables "as serving devotional purposes."

The symposium in Liblice, near Prague, was for some of us the first crossing of the "Iron Curtain." Milan Hašek's sonorous voice celebrating worldwide humanism charmed males and females alike. I recall with much pleasure listening to Ray Owen, then an inveterate pipe smoker, blowing superb smoke rings while, walking down from the Hradshin under a deep blue summer sky, the sun reflected from the many domes and cupolas of old Prague. Toward the symposium's end, Peter Gorer voiced the outlandish proposal to alter Transplantese: "homo-" to "allo-," "hetero-" to "xeno-." Was it then that Peter Medawar said that the present meeting would likely be the last time that each and everyone wanting to transplant human kidneys could be fitted into a single room?

A second Ciba conference, again in London, took place soon thereafter, I believe, at the Royal College of Pharmacists, with much construction underway at that time. I recall the serving of dry sherry at the first get-together, a highly recommendable custom then new to me, but unforgotten since. An outstanding report was that of J.F.A.P. Miller on post-thymectomy non-specific tolerance, one of the basic observations giving rise to modern immunological thought. Post-thymectomy tolerance of skin grafts first appeared difficult to accept, and my own dubious thoughts seemed to gain substance from the later report of a group whose name I happily forgot, which was unable to confirm Miller's claim; it turned out that they had removed salivary glands instead of thymuses. Peter Medawar also kindly referred to the "totally unexpected finding" of Y-chromosome-related skin graft rejection - an event that almost certainly had occurred, but not been noticed, many times previously. This was a chapter in itself, as was the founding of the *Transplantation Bulletin.*

I had since moved to Great Falls, Montana, as a practicing pathologist, and established a "Laboratory for Experimental Medicine," generously supported by NIH funds (*those* were the days!). Because of later insolvable (nonfinancial) conflicts with my hospital, Jack Stimpfling (who joined me from Bar Harbor years later) and I each rented an abandoned grocery store that still had shelving (usable for mouse colonies!) and counters (usable as work benches, though a mite high). There was running water, and power was easily reconnected. What more does one need? I remember an NIH site visit which yielded continued funding, possibly based on compassion and recognition of "A for Effort." This preceded the McLaughlin Institute, which for many years became the source for recombinant- and congenic-resistant mouse lines under Jack's stewardship. Tom Starzl, then still in Denver, presided over its initiation. At present it is facing major expansion, both structurally and spiritually. At the second Ciba conference, a proposal arose for a mouthpiece devoted to rapid and informal publication of transplantation data, and Herb Conway, plastic surgeon from Cornell, Nat Kaliss from Bar Harbor, and I were proposed as the editorial staff. Nat and I became good friends, and I shall not forget an evening of Mozart chamber music in Bar Harbor, Maine: Nat's wife was a concert pianist, and Jack Stimpfling's wife, Helene,

1951 Front, left to right. Author, "Bud" Silmser, Irv Weissman

1981 Irv Weissman, author

a respectable clarinetist, so they made up for my deficiencies on the viola.

Initially, the editorial office of *Transplantation Bulletin* was located in my Montana laboratory, and it would be difficult to imagine a more threadbare, informal operation - an affair of truly shoestring character. During the first nine months, all manuscripts and correspondence pertaining thereto were housed in a single (used) manila folder. I want to mention David Steinmueller, who years later, after my return to Utah in 1968, provided the needed energy, knowledge, and devotion to bring its successor, *Transplantation*, up to its present standard; upon David's departure, the journal was taken over skillfully and successfully by Tony Monaco and Mary Wood - not to forget the European office admirably established and administered by Leslie Brent, Richard Batchelor, and others.

A number of rocky episodes occurred in the history of the *Transplantation Bulletin*, largely of a financial nature. For a number of years under the guidance of Lyndon Peer, an unhappy marriage with Plastic and Reconstructive Surgery was brought on. Lyndon was a successful plastic surgeon from New Jersey whose fame, according to the jacket of a multiauthor book, rested on being the "inventor of diced cartilage."

The events leading to the description of the "male-specific skin rejection" ("H-Y", Eichwald-Simser factor") have been described in *Human Genetics* (vol. 58, pp. 1-127, 1981) on the occasion of a conference sponsored by the Kroc Foundation on "Errors of Sex Determination." It took place from October 8-12, 1980, in the beautiful hills of Santa Ynez, California, adjacent to Ronald Reagan's abode. Food was magnificent, the wines superior, and Scotch, Bourbon, Canadian Club, and other health foods were available from faucets in the wall of the dining area. Investigative endeavors covered a broad spectrum, from the "Etiology of Maleness in XX Men" discussed by de la Chapelle from Helsinki, to the genomic environment of H-Y including its 2005 base pairs, each of which may not presently be remembered exactly by everyone in the audience - although recalling the obvious formula

$$a=(g/2)n1\ (l-g/2)n2 \times N$$

should have facilitated this task. Susumu Ohno from the City of Hope presented these data; a man of inordinate intellect, he had been one of our early Montana visitors as he tried, with our inadequate equipment, to improve our method of Y-identification in chromosomal spreads. His human kindness and infinite patience (which made him suffer fools gladly) is reflected in the attached quote from one of his letters:

"In answer to your questions:

1 and 2. Type II male or female is trisomic for that part of the Linkage Group I autosome which is transposed to the X. In our paper, we reported studies on both Type I and Type II males. Your male, however, is Type II. The following diagram should clarify the matter (Fig. 1).

3. The male carries only one X; therefore, the male is "hemizygous" for any of the X-linked genes."

Luck, ignorance, and serendipity combined in the detection of H-Y; our only contributions of merit were the unwillingness to accept an unexpected observation and a meticulous bookkeeping system. The nimble hands of "Bud" Silmser, without any college exposure, enabled him to design a

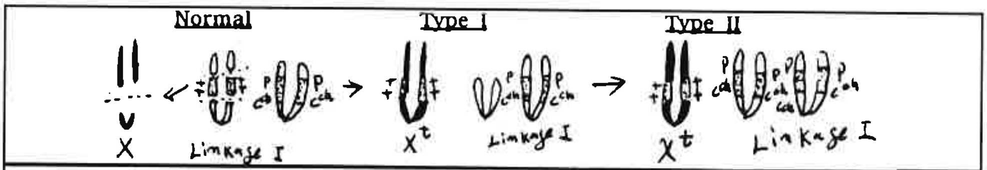


Figure 1. Normal, Type I, and Type II males (in Ohno's letter).

practicable way to skin graft mice, then a relatively new procedure. He had been selling second hand refrigerators in the basement of Montgomery Ward prior to joining me. He was clearly motivated by fear of losing his job if proven unable to make *all* syngeneic skin grafts succeed; in that, he failed (Table 1). As an aside, Bud had managed to sire 10 daughters in a row, and one may wonder what had happened to his own Y spermatozoa.

Table 1. "Bud's" skin graft success.

	M→M	F→F	F→M	M→F
C57BL to C57BL	11/11	12/13	6/7	0/11
A/Jax to A/Jax	7/7	9/9	3/3	10/18
A/Jax to F1	8/9	3/3	7/8	0/8
C57BL to F1	4/4	4/4	9/9	0/9

M=male
F=female

Prior to moving into abandoned grocery stores in Great Falls, Montana, we had the pleasure of assorted eminent visitors, attracted by the H-Y matter and, presumably, to see a relatively unknown section of this country. Milan Hašek was one of the early ones who, in his unmistakable Czech accent, conveyed to fellow customers in a bar that Montana was "beeeg, beautiful, clean, but not very clean - just like home." Leslie Brent showed us how to inject newborn mice intravenously. He confessed that he was a "softy at heart" and therefore did not like to bleed mice from their orbits. One day later while sitting on a rock at the Middle Fork of the Flathead River, south of Glacier National Park, he mentioned that newborn mice when injected with allogeneic spleen cells frequently failed to thrive, becoming runts, and he wondered whether this could be due to a reaction of the injected cells against the recipient - an idea which struck me as fairly bizarre. Bernard Amos also came with his family and commented on the magnificent bacon and egg fragrance at breakfast in our home. There was an unforgettable evening campfire with Ray Owen and Irv Weissman on the top of Rogers Pass. We took Gjoren Moller on a kayak ride down the Missouri River. Roy Calne and his wife were also subjected to a brief kayak trip under gray, rainy Montana skies. At that time he was a surgery resident at the Brigham Hospital, just beginning his impressive career.

The National Academy of Sciences also established a transplantation committee initially chaired by Lewis Thomas. The membership was widely representative; I was most impressed by Ray Owen, who had first described chimerism in fraternal cattle brought about via placental vascular anastomoses - an event which has been recognized as a cause of disease in newborn humans. After a year or less, Lew's term ended, and I was offered the committee's chair - presumably because I was neutral with respect to conceivable rivalries between various eastern centers. I remained in this position for some 12 years when, toward the end, Sherwood Lawrence from NYU took over; I had always admired "Sherry" very much. On an "invitation only" basis, the committee organized small symposia on assorted biological and medical transplantation subjects, the minutes of which were published but probably not widely read or distributed. My whole contribution to these events was minimal. One day, Bernard Amos committed an unusual crime, the opposite of what investigators at times accuse each other of doing (stealing data, staking claims, etc.). He wrote "Introductory Remarks" to one of these sessions signed "by Ernst J. Eichwald." I never talked to Bernard about it.

In general, these discussions were at a high level and not always easy to follow. I recall at one of the symposia when the speaker projected numerous slides in a darkened room, Walter Burdette, who was sitting next to me, nudging me gently; while slouching in my chair - soundly asleep - my wallet had slipped out of my pocket and fallen onto the carpeted floor. Hilary

Koprowski, always full of new ideas, first conceived the need for a thymus conference while we were at his gracious home attempting to play four-handed piano (he was very good), and Hilary was quoting from the Three-Penny Opera: "Erst kommt das Fressen...".

After one of these symposia, Joe Murray and I walked across the street to the National Gallery, and began a lasting friendship. At an early cup of coffee in the Gallery's cafeteria, I tried to explain to Joe the "Laws of Transplantation" and to convince him that any attempt to transplant kidneys in man, except between identical twins, was doomed to failure. He was not a good listener. Years later, he and his lovely family visited us in Montana. When we visited "Bud" Guthrie, author of "The Way West" and much additional successful western fiction, I introduced Joe as "the inventor of the human kidney." "Bud" was duly impressed.

Joe once mentioned that his true ambition in life was to become an expert brick layer or stone mason. In light of recent events, should one conclude that his career has been a failure?

Joe also let me watch one of the kidney transplants at the old Brigham Hospital, an institution I had always watched wistfully with awe and admiration from across the street at Childrens'. Some time earlier, I had tried to get into their pathology training program, then under the stewardship of the successful and vigorous Walter Sheldon, with whom I shared a Germanic background. His most widely quoted instruction to his residents was: "Take zin reprezentative zections of ze zymus."

Earthy language apparently was not then barred from the Brigham's august halls. I recall that one morning in the basement next to Radiology, a burly Irish orderly pushed a stretcher into the flank of the recently appointed Chairman of Internal Medicine, George Thorn, who was youthful-looking and blessed with a good crop of red hair. The orderly bellowed: "Get your butt out of the way, Pinky!" - except he did not use the term "butt." Likewise, upstairs in the operating room during a transplant procedure, the recipient was fully prepared for the kidney from the living donor next door, but nothing arrived. Finally, after waiting for some 20 minutes, the donor's surgeon entered, threw up his hands, and exclaimed: "I can't get the......thing out!" I was appalled.

There was much activity aimed at widening the narrow constraints of the National Academy meetings, as well as those of the editors of the liberated and rebaptized *Transplantation*. William Damashek of Boston, assisted by Robert Schwartz, wanted to participate, expand, or whatever, and he certainly had an "iron hand in a velvet glove," as one of our friends phrased it. I presume that the *Transplantation Proceedings*, ably developed and administered by Felix Rapaport, was the outcome of these endeavors. The small size of our conventional symposia was first broken by the large thymus meeting in Minneapolis, essentially directed by Robert Good. Sitting at my right side at his first meeting was Irving Weissman, then still in high school and a student in my Montana laboratory; this was the first, but clearly not the last, meeting at which he spoke during the discussion periods. Sitting at my left was another eager young man listening intently to the description of the technique of bursectomizing chickens by the anal approach and during the following discussion, asking for advice on how to bursectomize a hippopotamus. That was also the time when chairmen began to permit the popping of flash guns during scientific presentations, when news reporters were ever-present and when public relations offices were established.

Irv had been one of the first senior high school students in our laboratory, an activity sponsored by the Montana Cancer Society. Later, others from Great Falls High School became trainees in his laboratory at Stanford and have achieved fame of their own. Prior to one of our laboratory picnics in the Montana hills, an attractive student nurse from our hospital asked my permission for her brother (interested in "science" as a high school student at a very small northern Montana town) to visit our laboratory and to attend our picnic. His name was Lee Hood, later Chairman at Cal Tech and one of the world's outstanding immunochemists. He did attend both laboratory and picnic - and probably shouldn't have since both Irv and Lee then had their first beers, but that is a story that does not belong here.

The issue of forming a transplantation society arose in those years. Bernard Amos was one of its protagonists. I was apprehensive and passively resisted it. Without question, the move carried the day and was one of the elements shaping the extraordinary dynamism of today's transplantation world. Clearly, there were advantages, but I still question whether some of the goings-on at our present congresses - including a registration fee of almost $500 - are the way to go.

And yet, without the Society, without Congresses, news releases, and flashing light bulbs, one wonders whether the considerable number of fellow human beings kept alive by transplanted hearts or kidneys would exist today. Without these endeavors, I could not have experienced the sublime pleasure, one night at 3 AM in our hospital, of seeing for the first time the removal of a beating human heart - still a troubling and jarring experience - but followed by placement of the transplant, lying still and cold in a container but then turning pink, beginning to twitch, and then to pulsate. As the saying goes, it was a pleasure. All of it. It will continue to be a pleasure if we follow Galileo Galilei's advice, in Bertold Brecht's "Life of Galilei."

"Yes we shall question each and everything, time and again. And we shall not make progress rapidly, but at a snail's pace instead. And what we detect today we shall wipe off the blackboard tomorrow, and we shall not write it down again until we have made the same observation independently over again. When we observe the sun we must do so with the indomitable desire to prove that it rotates around the earth, and that the earth is at rest. And only after we have failed, failed completely and miserably, when we lick our wounds in sorrow, only *then* shall be begin to ask ourselves whether we are maybe right when we assumed that it is the earth which does the rotating."

CURRICULUM VITAE

Ernst J. Eichwald

PERSONAL

Born: December 13, 1913; Hannover, Germany
Citizenship: United States

EDUCATION

1938	University of Freiburg, Germany, M.D.
1953	University of Utah College of Medicine, M.D.

MEDICAL LICENSURE

1939	New York
1940	National Board of Medical Examiners
1947	Massachusetts
1954	Montana
1968	Utah
1947	Certified by American Board of Pathology, Pathological Anatomy

MILITARY SERVICE

1938	German Wehrmacht
1944-46	United States Army Medical Corps, Pacific Theater

POSITIONS

1938-39	Intern, St. Elizabeth Hospital, Covington, Kentucky
1939-40	Intern, Good Samaritan Hospital, Dayton, Ohio
1940-42	Resident, Pathology, St. Elizabeth Hospital, Dayton, Ohio
1942-43	Resident, Pathology, Children's Hospital, Boston, Massachusetts
1943-44	Resident, Pathology, Free Hospital for Women Brookline, Massachusetts
1943-44	Lying-in Hospital, Boston, Massachusetts
1943-44	Assistant in Pathology, Harvard Medical School
1944-46	Chief of Laboratory Service I20 GH, United States
1946-48	Assistant Pathologist, Children's Hospital, Boston, Massachusetts
1946-48	Instructor in Pathology, Harvard Medical School
1948-49	Assistant Clinical Professor of Pathology University of Utah College of Medicine
1948-49	Chief of Laboratory Service, Veterans Administration Hospital
1949-54	Associate Professor of Pathology University of Utah College of Medicine
1949-54	Cancer Coordinator, University of Utah College of Medicine
1952-54	Founder and Director, Utah Tumor Registry

1954-65	Founder and Director, Laboratory for Experimental Medicine Montana Deaconess Hospital, Great Falls, Montana
1954-65	Director of Laboratories, Montana Deaconess Hospital Salt Lake City, Utah
1966-67	Director, McLaughlin Research Institute, Great Falls, Montana
1966-68	Professor of Microbiology, Montana State University
1968-79	Professor and Chairman, Pathology Department, University of Utah
1968-	Professor of Surgery, University of Utah
1968-	Professor of Pathology, University of Utah

PROFESSIONAL SOCIETIES

1952-54	Educational Chairman, Utah Cancer Society	
	Tissue Transplantation Committee, National Academy of Sciences National Research Council	
	1957-	Member
	1958-68	Chairman
1959-61	President, Montana Pathological Society	
	Montana Cancer Society	
	1960-66	Fellowship Chairman
	1966-68	President
1961-63	Program Chairman, Montana Medical Association	

AWARDS

1984	January "Transplantation" issue in honor of Ernst Eichwald, as "Eichwald Festschrift"

EDITORIAL BOARDS AND EDITORSHIPS

1953-62	Editor, Transplantation Bulletin
1956-58	Member, Editorial Board, Cancer Research
1962-	Editor, Transplantation
1963-67	Member, Editorial Board, Rocky Mountain Medical Journal
1968-75	Member, Editorial Board, Proceedings of the Transplant Society
1968-76	Member, Editorial Board, Progress in Transplantation

PUBLICATIONS

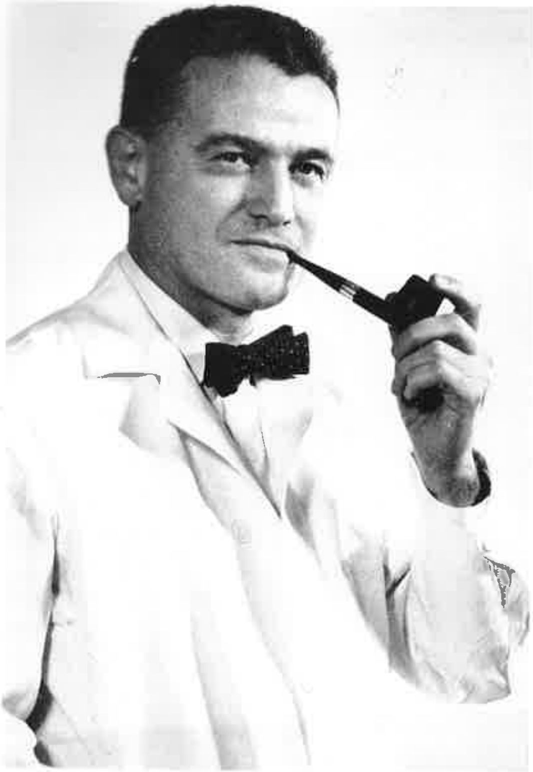
Total: 104

EARLY EXPERIENCES IN KIDNEY TRANSPLANTATION

Willard E. Goodwin

Address: UCLA School of Medicine
Division of Urology, Room 66-128, CHS
Los Angeles, California 90024

Willard E. Goodwin



1959

1987

EARLY EXPERIENCES IN KIDNEY TRANSPLANTATION

Willard E. Goodwin

Memories, memories! It is a little difficult but a pleasant moment to try to recall events and thoughts of more than 40 years ago, but here are some reflections on my interest and activity in renal transplantation at UCLA and elsewhere. These notes must, of necessity, be very personal.

The idea of renal transplantation was something that first intrigued me in the 1940s when I was working in the experimental laboratories of W.W. Scott at Johns Hopkins. I conceived and performed some crude experiments, extremely simple, and not original. I was thinking of an artificial kidney and decided to try experiments with cross-transfusions.

We made "dog A" uremic and then cross-transfused him with a healthy "dog B." This clearly showed that B's kidneys would soon clear the uremia. My friend, Hank Bahnson, was kind enough to come up to the laboratory and show me how to anastomose the carotid artery of "A" to the jugular vein of "B," so the experiment was easily done. It was simple and primitive, but I was "hooked" on the idea that it might be possible to use a second source for a kidney.

In 1951 I was fortunate enough to become the first urology professor in the dynamic surgical department of Dr. William P. Longmire, Jr., at UCLA. Dr. Longmire had a long-standing interest in transplantation (1). In his laboratory, at that time, Drs. Jack Cannon and Paul Terasaki were working on transplanting chick embryos. It was considered "respectable."

When I announced that I would spend my first sabbatical on kidney transplantation, no one objected. However, my most knowledgeable friends said, "Don't waste your time on the kidney, skin is where the action is." (2)

Nonetheless, I felt that if there were to be a breakthrough it could come with an integrated organ such as the kidney. Further, as an urologist, I felt strongly (and have written) "The kidney begins at the aorta and most problems before and after transplantation are urological and belong in this sphere." This should be part of the competency of the well-trained urologist and not in the hands of amateurs.

After I read Hume and Merrill's pessimistic report concerning homologous transplantation of human kidneys (3) and learned of the stunning success of the first permanent successful kidney transplantation between identical twins by Merrill, Murray, Harrison, et al (4), I was intensely interested in the future prospect of kidney transplantation and thus decided to take my first sabbatical leave in 1958 and 1959 to focus on this problem. The first half of that year was to be spent in Boston and the second half in Edinburgh.

In April 1959, I wrote the following "Urologists' Correspondence Club Letter" from Edinburgh (5). It was sent as an informal message to many American urologists. In part I wrote:

"Some of you who share my admiration for Osler's essays will recall the following words from *The Student Life*: 'The third essential for the practitioner as a student is the quinquennial brain-dusting, and this will often seem to him the hardest task to carry out - Hearken not to the voice of old Dr. Hayseed, who tells you it will ruin your prospects, and that he never heard of such a thing as a young man, not yet five years in practice, taking three months holiday. To him it seems preposterous. Watch him wince when you say it is a speculation in the only gold mine in which a physician should invest - Grey Cortex!'

"September 1958 to September 1959 is the period for my brain-dusting. From September through January last I was in Boston, working with Doctor Joseph Murray in the Laboratory for Surgical Research. (This is Professor Francis Moore's Department of Surgery at Harvard Medical School and the Peter Bent Brigham Hospital.) At present (from February to August) I'm working in the Wilkie Laboratory of the Department if Surgical Science at the University of Edinburgh (under the direction of Professor M.F.A. Woodruff*). In both places it has been a pure laboratory experience, without clinical responsibilities.

"The problem that seemed most interesting, and possibly solvable within my lifetime (by others, not by me), is the matter of trying to achieve successful transplantation of living tissues from like but not identical members of the same species (homografting). This interest led to the choice of Boston and Edinburgh as places to work, for important basic advances are being made in both these centers as well as in the Department if my Chief (Professor William P. Longmire, Jr., in the Department of Surgery at UCLA).

"The experience in Boston, where we worked chiefly on kidney transplantation in the dog, was enormously instructive and rewarding (6). The work here in Edinburgh, where we're grappling with attempts to produce tolerance to grafting by lethal X-rays in rats, rabbits, and dogs, promises to be equally interesting and informative. The problems are far from solved, but many advances have been and are being made. It is wonderfully exciting, like scaling an unfamiliar and difficult mountain with the summit in plain view bathed in sunshine, while the climbing party below uncertainly and anxiously scans the various possible routes ahead, dimly seen in mist and shadow, and discusses which path is the most likely to succeed with the least peril and suffering.

"In Boston I had the added pleasure of making weekly urology rounds with Hartwell Harrison and his staff at Brigham and of attending some of the teaching conferences with Wyland Leadbetter and his staff at the Massachusetts General Hospital. Both of these teaching services are of the first rank, and it was a distinct privilege to observe these Bostonian gentlemen 'at home' as it were. I learned a great deal.

"One of my primary aims at the Brigham was to observe one of the kidney transplantation operations which have been successful in identical twins. Fate, and Joe Murray and Hartwell Harrison, were kind; and I was privileged to observe two of these famous procedures (the 9th and 10th in their series, I believe). The details are too complex to recount here, but both procedures were most impressive. They were done with consummate skill, 'deliberate speed' and elegant technique. Both pairs of twins have done well.

"The second twins (treated surgically in January 1959) deserve special mention, as they were probably not quite identical. The situation was desperate for the sick one; however, and his well brother almost demanded that he be allowed to give his healthy kidney. This was finally done, after much discussion, and after the sick twin had been given two sublethal doses of irradiation to depress his immune responses. The immediate result has been successful, and the sick twin is now living on his brother's kidney after having both of his own diseased kidneys removed.

"Lest you all feel the urge to run right over to the hospital and try this, may I say that I left Boston with the firm conviction that this extremely difficult problem could probably have been handled as it was, successfully, in only a very few places. Certainly the skill and experience necessary for this procedure, not only in the actual surgery but also in all that leads up to it and follows after, is not easily come by.

"One of the things that most impressed me about the 'kidney group' at the Peter Bent Brigham was the beautifully developed sense of team work and group action. Doctor John Merrill, internist, is a kind of 'anchor man.' He keeps the severely uremic twin alive with judicious use (or not use) of the artificial kidney while the stage is being set for surgery and the necessary consultations and deliberations are in progress. There is an air of urgency but not of screaming, blind emergency. Doctor Hartwell Harrison, urologist, removes the healthy kidney from the well twin after careful and meticulous dissection without harm to the precious organ. Doctor Joseph Murray, plastic surgeon, performed the actual transplant (left renal artery to right hypogastric artery, end to end; and the left renal vein to right iliac vein, end to side). Together Harrison and Murray perform the necessary ureteroneocystostomy, using a tunnel technique with direct anastomosis of the ureteral stoma to bladder mucosa through the open bladder.

"The decisions concerning if and when to operate on these patients are made after thoughtful group discussion by Doctors Harrison, Merrill, Murray, Dealy (Professor of Radiology) and Moore (Professor of Surgery). It is a superb example of purposeful team work throughout. The legal problems of consent, etc. are considerable and need special consideration and sometimes court action before this type of transplantation can be undertaken (3)."

That letter was a description of my first sabbatical year which proved a very fertile experience. My work at the Brigham was reported with Balankura, Murray, and Dammin, in Surgical Forum, 1960 (6). Our experiment was a simple one but certainly lead to a quick understanding of the technique of renal transplantation. Balankura and I took the kidney from dog A and put it in dog B and then, likewise, a kidney from B and put it into A, and then a day later we would go back and retransplant that kidney in the original owner. Then we would lengthen the period before retransplantation in further experiments. What we wanted to see was what kind of changes would take place in time if the kidney was replaced in its original owner. It was not a very important experiment, but it certainly gave a lot of experience in technique.

In October 1959, my friend, Clarence Hodges, called to ask if I would come to Portland to participate in a kidney transplantation between identical twin girls. I told him I would be happy to make the trip but that I didn't think I wanted to be responsible for doing that for the first time in a human being, outside of my own bailiwick. The transplantation was then arranged by Bert Dunphy and Hodges, with Joe Murray to come out from Boston (7). Those twins are still alive and well. This further increased my excitement and expertise. Later on I was able to perform the first identical twin kidney transplantation in southern California in July 1961 (8).

These were, indeed, new horizons. This was before we had any proven drug to suppress rejection. It was before Imuran. There was a great deal of uncertainty but we plowed ahead slowly, searching for clues. As far as I know, no urologists, other than Hartwell Harrison, in Boston, and I, were working on the problem at that time.

By 1962 we were able to report the lessons we had learned in our first six cases at UCLA (9). These were done before any good antidepressant drug was available and before Imuran.

In case No. 3 (September 1960), we described, with Dick Glassock and Morton Maxwell, the first patient who was to receive nitrogen mustard (cytoxan) to suppress the rejection reaction, and also, I believe, to be *the first reported reversal of rejection with massive doses of prednisone* (9).

In our sixth case, October 1961, we also described the first human use of "en bloc" technique of transplantation of both kidneys with a segment of aorta and vena cava removed from a stillborn anencephalic monster (9). That case was a failure because the blood supply never did open up, but it was later successfully done elsewhere.

In 1963 I was asked to address the American Urological Association on kidney transplantation. In part, I said the following (10):

"A final solution to homograft rejection still eludes us. Yet the topic becomes more interesting and more important each day. At a recent surgical meeting, Hume said 'renal transplantation is now coming of age.' We agree, and 1963 may well be the year of decision in developments in this field. Though there are as yet no permanent successes of kidney transplantations except between twins, many men working on the problem feel that a breakthrough could be 'just around the corner.'

"It is a particular pleasure to speak to my fellow urological surgeons regarding this vital subject-as by training, experience and interest you are, should, and must be interested and intimately involved in the rapid developments and advances in this field of renal surgery. I am honored to address this distinguished audience on the subject of homotransplantation; yet I feel a little inadequate. Doctor Hartwell Harrison, at the Peter Bent Brigham Hospital in Boston, should be your speaker."

In 1963, we also reported and described the first use of ureteropyelostomy or pyeloureterostomy which we employed in our 9th case of kidney homotransplantation (10,11).

We were slowly feeling our way with new ideas and variations. It occurred to us that we might do a transplant between identical twins where one had a very bad urinary tract tuberculosis, and we had the thought of either diverting the urine or enlarging the bladder, although we never did this. We also considered the possibility that the urinary tract might later be used as an outflow passage for other body fluids if people ever got around to doing pancreatic transplantation, for instance. We had thought of all of these things but didn't try any of them at that time.

In 1967, the International Society of Urology met in Munich and I was invited to address them and summarize the experience of kidney transplantation from North America. At that time this was a labor of love because things were moving so fast. I was able to collect more than 900 kidney transplantations reported by North American surgeons at that time (12,13).

With Dr. Joseph Kaufman, in 1967, we reported the second case of successful normal childbirth after kidney homotransplantation. Both mother and child did well (14). Her transplantation was in 1965, and she delivered a normal baby, September 17, 1966. We had been "scooped," however, by Hume, et al, who described the first normal delivery at term after kidney transplantation. Their patient had delivered in April 1966 (14).

Later in 1967, Donald Martin and I described a patient who had terminal uremia from polycystic renal disease. This patient had a kidney transplantation, and the original kidneys were left in. They were observed to *shrink in size*, and the patient developed polycythemia vera (15).

In the beginning, I did most of the transplants myself, but, as noted, soon Joe Kaufman and Don Martin became involved. When I went on another sabbatical about that time, I left Donald Martin in charge of the transplant program at UCLA. He has since carried on with remarkable facility and many contributions in his position as Professor of Urology at the University of California/Irvine.

During all this time, Paul Terasaki was busy with serological typing and sorting out all the various complications and combinations (16). He put it on a firm footing at UCLA, and his contributions are now universally recognized and used everywhere that transplantation is being done. With his contributions, the use of cadaver kidneys from unrelated donors became more practical (16,17). Serological typing is now a universal practice as is also the use of steroids to block and control rejection reactions. These were unforgettable times, indeed! (18,19)

Before we understood the extreme importance of Terasaki's serology matching techniques, and, indeed, before we had results of a particular case, we were caught and embarrassed in what was probably the "first documented case of a hyper acute rejection detected by a crossmatched test (20)." We had scheduled a transplant from brother to sister to be shown on television for a meeting of the California Medical Association in downtown Los Angeles. It was carefully planned, with Joe Kaufman acting as moderator in the operating room, and Ralph Goldman, acting as moderator in the viewing room in downtown Los Angeles. Although the procedure was technically perfect, we were unaware of the findings from Terasaki's laboratory which predicted an hyperacute rejection, and we saw the rejection occur before our eyes at the end of the operation.

Hume's prophecy, "real transplantation is now coming of age" had proved to be correct.

I was grateful for my sabbatical year experience and the opportunity to participate and grow with the subject which followed my sabbatical year in 1958 and 1959.

The present situation is much more refined. We have teams working on transplantation, and at UCLA we have a full-time kidney transplant surgeon, Tom Rosenthal (21,22).

In most big centers there are transplant teams which not only exchange information but deal with transplantation of hearts, lungs and the pancreas, as well as kidneys from the same cadaver donors.

Dr. John Barry, Professor at the University of Oregon, has organized team training of community urologists and general surgeons to perform cadaver kidney transplant retrievals (23). He has developed a remarkable system which works throughout Oregon. The concept, I think, is one that will catch on and be used elsewhere. I think we are in a remarkable period of expansion and can look forward to an even more active future.

REFERENCES

1. Longmire WP, Jr, Stone HB, Daniel AS, et al. Report of clinical experience with homografts. Plast Reconstr Surg 1947; 2:419.
2. Goodwin WE. Recollections: Early experiences in kidney transplantation. Transplant Proc 1981; 13:1.
3. Hume DM, Merrill JP, Miller BF. Experience with renal homotransplantation in the human: report of nine cases. J Clin Invest 1952; 31:640.
4. Merrill JP, Murray JE, Harrison JH, et al. Successful homotransplantation of the human kidney between identical twins. N Engl J Med 1960; 262:1251.
5. Goodwin WE. I. A sabbatical 'brain dusting.' II. Problems of tissue transplantation. Urologists' Correspondence Club; June 19, 1959.
6. Balankura O, Goodwin WE, Murray JE, et al. The study of the homograft reaction by retransplantation of the canine kidney. Surg Forum 1960; 11:24.
7. Hodges CV, Pickering DE, Murray JE, et al. Kidney transplant between identical twins. J Urol 1963; 89:115.
8. Goodwin WE, Mims MM, Kaufman JJ, et al. Human renal transplantation. II. A successful case of homotransplantation of the kidney between identical twins. Calif Med 1962; 97:8.

9. Goodwin WE, Kaufman JJ, Mims MM, et al. Human renal transplantation. I. Clinical experiences with six cases of renal homotransplantation. III. Technical problems encountered in six cases of kidney homotransplantation. J Urol 1963; 89: 13,349.

10. Goodwin WE, Martin DC. Transplantation of kidney, Spring 1963. Urol Survey 1963; 13:229.

11. Goodwin WE. Ureteropyelostomy or pyeloureterostomy - 1962. Urology 1977; 10 (suppl):4.

12. Goodwin WE, Martin DC, Kaufman JJ, et al. Kidney transplantation in the USA (January 1967). Proc 14th Intl Cong Urol, Munich, July 9-14, 1967.

13. Goldman R, Goodwin WE, Kaufman JJ, et al. Sixteen cases of renal homotransplantation. Arch Intern Med 1964; 114:601.

14. Kaufman JJ, Dignam W, Goodwin WE, et al. Successful, normal childbirth after kidney homotransplantation. JAMA 1967; 200:338.

15. Martin DC, Goodwin WE. Renal transplantation in polycystic disease. JAMA 1967; 202:654.

16. Terasaki PI, Vredevoe DL, Mickey MR. Serotyping for homotransplantation. X. Survival of 196 grafted kidneys subsequent to typing.Transplantation 1967; 5:1057.

17. Smith RB, Martin DC, Terasaki PI, et al. Experience with forty-seven renal homotransplantations from cadaveric donors with emphasis on donors with marginally acceptable kidneys. Am Surg 1969; 35:1.

18. Martin DC, Goodwin WE, Kaufman JJ, et al. Kidney transplants: ninety-two cases, results, lessons learned, future prospects. J Urol 1968; 100:227.

19. Russell PA, Cosimi AB. N Engl J Med 1979; 301:407.

20. Terasaki PI, Marchioro CH, Starzl TE. Serotyping of human lymphocyte antigens: Preliminary trials on long-term kidney homograft survivors." Natl Acad Sci - monograph on histocompatibility testing, Washington DC, 1965; 83.

21. Rosenthal JT, Ettenger RB, Ehrlich RM, et al. Technical factors contributing to successful kidney transplantation in small children. J Urol 1989; 144:116.

22. Rosenthal JT, Miserantino DP, Mendez R, et al. Extending the criteria for cadaver kidney donors. Transplant Proc 1990; 22(2):338.

23. Barry JM, Hefty TR, Nelson KA, et al. Ten years of training community urologists and general surgeons to do cadaver kidney retrievals. J Urol 1990; 143:897.

CURRICULUM VITAE

Willard E. Goodwin

PERSONAL

Born: July 24, 1915; Los Angeles, California
Marital Status: Mary Pearson Josephs, 1942
Children: Mary D. Cabot (1943), Peter Colt Goodwin (1945, deceased), Willard Goodwin II (1948)

Home Address:
254 Bronwood Avenue
Los Angeles, California 90049

Office Address:
UCLA School of Medicine
Division of Urology, Room 66-128, CHS
Los Angeles, California 90024

EDUCATION

1937	University of California, Berkeley, A.B.
1941	The Johns Hopkins University School of Medicine, M.D.

BOARD CERTIFICATION

1951	American Board of Urology

MILITARY SERVICE

1942-46	Army of the United States, Medical Department

POSITIONS

1941-42	Intern, The Johns Hopkins Hospital
1942	Pathologist, The Johns Hopkins Hospital
1946-48	Assistant Resident, The Johns Hopkins Hospital (James Buchanan Brady Urological Institute)
1947-48	National Research Council Fellow
1948-49	Resident, Brady Urological Institute
1948-50	Instructor in Urology, The Johns Hopkins University School of Medicine
1950-51	Assistant Professor of Urology, The Johns Hopkins University School of Medicine
1951-53	Associate Professor of Surgery and Chief, Division of Urology, University of California School of Medicine, Los Angeles
1953-70	Professor of Surgery and Chief, Division of Urology University of California School of Medicine, Los Angeles
1970-	Professor of Surgery, Urology
1986	Professor Emeritus
1983-86	Distinguished Physician, Veterans Administration Medical Center Sepulveda
1986-88	Distinguished Physician,Veterans Administration Medical Center Sepulveda, Reappointment

HOSPITAL AFFILIATIONS

Urology, University of California Medical Center, Los Angeles
Consultant, Urology, Wadsworth Veterans Administration Medical Center, Los Angeles
Consultant, Los Angeles County Harbor General Hospital, Torrance
Honorary Consulting Staff, Santa Monica Hospital, Santa Monica
Courtesy Staff, St. Johns Hospital, Santa Monica
Courtesy Staff, The Hospital of the Good Samaritan, Los Angeles
Consulting Staff, Urology, Cedars-Sinai Hospital, Los Angeles

PROFESSIONAL SOCIETIES

American Board of Urology
  1975-81 Trustee
  1977-79 Chairman, Credentials Committee
  1977-79 Vice-President
  1980-81 President
Alpha Delta Phi
Alpha Omega Alpha
1972-73 President, American Academy of Pediatrics, Urology Section
1982-83 President, American Association of Genito-Urinary Surgeons
American Osler Society
American Surgical Association
American Urological Association
Association of American Medical Colleges
Bay Surgical Society
1977-78 President, California Society of Genito-Urinary Surgeons
Los Angeles County Medical Association
Los Angeles Surgical Society
1969-70 President, Los Angeles Urological Society
Pacific Coast Surgical Association
Pan American Medical Association
Sigma Xi
1977-80 President , Societe Internationale d'Urologie, U.S. Section
1976-77 President, Society for Pediatric Urology
Society of University Surgeons
1976-77 President, Society of University Urologists
1983-84 President, Western Section of the American Urological Association
Western Urologic Forum (Founding Member)
Honorary Member, Alaska State Medical Association
Honorary Member, Chilean Society of Urology
Honorary Member, "Die Deutsche Gesellschaft fur Urologie"

	Honorary Member, Urological Society of Australasia
	Honorary Member, Urological Society of Rosario
	Honorary Member, British Association of Urological Surgeons
	Corresponding Member, "La Sociedad Venezolana de Urologia"
1981-82	Vice-President, American Association of Genitourinary Surgeons
	Honorary Member, Philippine Urological Association

AWARDS

1944	Soldiers' Medal
1953	Joseph F. McCarthy Prize Essay (with Kaufman and Rosenthal) of the Western Section, American Urological Association
1954	First Prize, American Urological Association in essay competition (with William Casey)
1978	The Barringer Medal, American Association of Genito-Urinary Surgeons
1978	The Hugh H. Young Award, American Urological Association
1978	Doctor Medicine Honoris Causa, Freie Universitat, Berlin
1978	Member, The Johns Hopkins Society of Scholars
1980	The Valentine Medal, New York Academy of Medicine, Urology Section
1980	Establishment of the Willard E. Goodwin Society
1986	Dedication of Harbor/UCLA Renal Transplant Program to Dr. Willard E. Goodwin
1986	Honorary Member of the Squier Urological Clinic
1986	UCLA Division of Urology "A Day of Tribute in Honor of Willard E. Goodwin, M.D."
1986	Honorary Member of the British Association of Urological Surgeons
1987	Keyes Medal, American Association of Genitourinary Surgeons
1990	Elected to Honorary Membership in the American Urological Association during the 1990 Annual Meeting
1990	St. Paul's Medal of the British Association of Urological Surgeons

EDITORIAL BOARDS AND EDITORSHIPS

Encyclopedia of Urology
Urolgoia Interanationalis
International Journal of Nephrology, Urology, Andrology

COUNCIL AND ADVISORY COMMITTEE MEMBERSHIPS

1974-78	American College of Surgeons, Advisory Council for Urology
1976-82	American Medical Association, Residency Review Committee

PUBLICATIONS

Total: 468

RECOLLECTIONS FROM THE LABORATORY TO THE CLINIC

Sir Roy Calne

Address: Department of Surgery
University of Cambridge Clinical School
Addenbrooke's Hospital
Hills Road
Cambridge CB2 2QQ
England

Sir Roy Calne

Recent

Self portrait

RECOLLECTIONS FROM THE LABORATORY TO THE CLINIC

Sir Roy Calne

My interest in transplantation began when I was a medical student, observing many fatal diseases in young people when all they required were new organs. I was particularly stimulated by the consistent lack of encouragement and negative response with which my naive suggestions were met. Taking care of a youngster about my own age with Bright's disease, in Guy's Hospital where Bright had worked, I was told by the senior consultant that we would have to make him as comfortable as possible for the two weeks of life which remained. I asked if he could receive a kidney graft and was told no; I then asked why not and was told because it cannot be done. I felt that further enquiry would be interpreted as rudeness so I did not persist. However, our group of students discussed the matter afterwards and apart from some science fiction vaguely recalled, there did not seem to be any information available. In fact we were wrong because in the early 1950s when this took place, a considerable amount of scientific work had already been done, particularly by Medawar and Gibson, on the nature of rejection of grafts. Working in Glasgow in the 1940s they had shown that skin grafts in rabbits were destroyed by an inflammatory process after initial vascularization and a second graft from the same donor was destroyed even more quickly, revealing the immune nature of graft rejection (1-3).

This was followed by similar experiments with kidney grafts by Simonsen in Denmark (4) and Dempster in England (5). It was only a few years later at the Peter Bent Brigham Hospital in Boston that Hume would report on the first functioning renal allograft in man (6) and Murray, Merrill, and Harrison would begin their program of identical-twin renal grafts (7).

As far as I was concerned that was the end of my initial personal probe into the subject and after serving with the Army in Hong Kong and Malaya, I returned to teach anatomy at Oxford and attended a science lecture given by Medawar in 1956 telling the exciting story of immunological tolerance, with beautiful illustrations. He had the audience spellbound with brilliant oratory and the content of his message. When he finished, a medical student asked if there were a potential application for the work; Medawar's reply was short, in fact two words, "Absolutely none!" I was amazed that he felt this way, having seen photographs of black skin grafts on white mice and white feathers on black chickens, and I was up until early in the morning arguing the subject with my brother who was a medical student at Oxford. At the end he declared that he was going to bed and that since Medawar was a world authority on the subject and had said there was no possibility of application, it was probable that he was right!

The next day, however, I was still unconvinced and asked the Head of the Department of Anatomy, Sir Wilfred le Gros Clark, who was a friend of Medawar, if he would write a letter recommending me to join Medawar's laboratory to study transplantation. Le Gros Clark informed me that Medawar was a very busy man and since I wanted to be a surgeon I had better go and learn how to do hernias. Shortly afterwards when I had passed the Fellowship of the College of Surgeons, I obtained a resident registrar post at the Royal Free Hospital in London and for the first time met somebody who thought that working in this field might be worthwhile. This was John Hopewell, a young, dynamic urologist who had facilities at the Buckston Browne Farm in Kent, the research establishment of the Royal College of Surgeons of England, where he was studying the metabolic effects of ureteric implantation into the bowel. He introduced me to Professor David Slome, head of the research establishment and Professor of Physiology. At that time there was no Academic Department of Surgery at the Royal Free Hospital or facilities for surgical research.

Professor Slome was, and still is, a great enthusiast but, unfortunately, he had no money to sponsor my research and I had no chance of obtaining a grant since I had a spectacular paucity of credentials. David Slome allowed me to attempt to transplant kidneys in rats. At that time no successful technique had been described and I started using plastic stents for the vascular junctions. After many late night hours of grappling with the technique, I eventually obtained kidney function for 24 hours, but it seemed unlikely that I would progress any further. One night, David Slome came into the laboratory and pointed out to me that I was persistently and consistently failing, but, since he was convinced that I was keen, he would let me transplant a kidney in a dog. I had read of the kidney transplantation technique published by Simonsen and Dempster, and although Dempster was still in London, he had a reputation for being a difficult man to approach. Therefore I did the transplant on my own, using an intra-abdominal technique very similar to that practiced clinically today. I was untrained in vascular surgery, the facilities were very primitive, and the surgical light was an "Ovaltine" tin with an ordinary bulb. The head technician, Mr. Watson, had worked with Dempster before he moved to Hammersmith Hospital and was very helpful.

My first attempt was successful as an autograft, with the animal surviving after removal of the other kidney, despite the fact that the period of warm ischemia was 90 minutes. David Slome was pleased with this result but disappointed to observe the next 10 technical failures. Eventually the technique was reasonably successful, and in the meantime I had studied the literature on transplantation which in 1959 could be done in a few weeks. Now a lifetime would not get one through half of the publications.

The clinical application of total body x-irradiation, by far the most popular method of depressing the immune response, had just been started with disastrous results, apart from two nonidentical twin transplants: one performed in Paris by Hamburger's group (8) and the other at Peter Bent Brigham in Francis Moore's Department (9). Professor Smithers at the Royal Marsden Hospital generously gave permission to use the new cobalt machine at the Surrey branch of the Royal Marsden Hopital, provided I worked at night when it was no longer needed by the patients. My knowledge of gamma rays was rudimentary and my practical experience nil. The senior technician in the cobalt unit showed me where the switches were, worked out the dose so I could start at 8 PM just as long as I was out by 8 AM, and she then went home. My wife helped me with these experiments in the cobalt unit, anesthetizing dogs and giving slow irradiation, first on one side and then on the other. X-irradiation of 900 rads produced severe depletion of the bone marrow with pancytopenia; the dogs were nevertheless able to reject their grafts aggressively, almost as quickly as nonirradiated dogs. To increase the dose to supra-lethal levels and give bone marrow grafts was too drastic and had been tried in man without success.

I wondered whether an alternative to x-irradiation might be the use of anticancer drugs. Dr. Ken Porter, a junior pathologist at St. Mary's, later to become Professor there, had worked at Peter Bent Brigham Hospital with Dr. Murray and had used Thiotepa to obtain modest prolongation of skin grafts in rabbits (10). I therefore contacted Dr. Porter, whom I had previously not met, and he invited me to tea at St. Mary's where he discussed his experiments and showed me a paper in that week's Nature by Schwartz and Damashek (11) who had prevented rabbits from producing antibodies against human serum albumin by treating them for two weeks with the antileukemia drug, 6-mercaptopurine (6-MP). Moreover, this effect persisted after the drug treatment had stopped. The animals were able to react normally against another protein antigen, bovine gamma globulin. We felt this was a much more promising approach than x-irradiation. Ken Porter and I decided we would each investigate 6-MP; he would study its effects on skin grafts in rabbits and I would see if it could prolong canine renal allografts.

I started these experiments in the summer and was pleased to note that some of the animals had prolonged renal allograft function. Mr. Watson was particularly impressed since he had seen several hundred kidney grafts performed by Dempster and none had functioned as long as the grafts in the 6-MP-treated dogs. When it was clear that 6-MP was an interesting compound, I telephoned Ken Porter; before I could give him my news he said, "You remember the 6-MP experiments, well it did not have any significant effect on rabbit skin allografts so I wouldn't bother to try it in the dogs." I was pleased that I had not heard this earlier, and it was the first clear indication to me of the variation in behavior to rejection of different tissues as well as species variation. This work produced a short paper which I submitted to the *Lancet* in November 1959 and was published in February 1960 (12).

Dempster wrote a strange letter to the *Lancet* in response to my report (13), which seemed to indicate that he did not entirely believe my results. This caused me distress since it was my first scientific paper and I was in a very junior position. I had an opportunity to discuss my work with Michael Woodruff who was encouraging and thought I ought to contact Peter Medawar. Despite having been warned about how busy he was, I telephoned his secretary and very meekly asked if I might sometime have a chance to speak to him. She said, "I'll put you through;" I was protesting "Oh no, no - he's a very busy man!" By then I was speaking to the great man who gave me the impression that he had all the time in the world and invited me to a colloquium - a new word for me - on the state of the art in tissue transplantation to be held at University College.

My introduction to biological science was a revelation. I met Gorer, Mitchison, and Brent; I was surprised by the generous, friendly atmosphere and discourse, even if there was strong disagreement. The open-mindedness and lack of dogma were in marked contrast to the hierarchical system of the surgical world.

My experiments seemed interesting to the experts, and I had a letter from Charlie Zukoski saying that he, working with Hume, had obtained similar results with 6-MP, although they had trouble with toxicity and dosage (14). In contrast to my other chiefs, John Hopewell was delighted with the results of these experiments and agreed to use 6-MP in clinical kidney transplantation. We had no experience of clinical kidney transplantation at the Royal Free in 1960 and dialysis was only just being set up by John Hopewell. The first patient we were planning to treat was a lady suffering from end-stage renal failure from polycystic kidneys and a potential donor was admitted with a subarachnoid hemorrhage from which she died. I prepared the iliac vessels in the recipient whilst in an adjacent operating theater, John Hopewell removed the donor kidneys. I thought all was going well when John Hopewell came into the operating theater with misery on his face, and in a dish he held the donor kidney he had removed, which was polycystic! I have since never forgotten the association of polycystic disease with berry aneurysms in the brain, which occur in about five percent

Arriving in New York, Roy, Patsy, Sarah, 1960.

Roy and Lollipop, Harvard Medical School, 1960.

Roy, Jane, and friend, Harvard Medical School, 1960.

of cases of subarachnoid hemorrhage. It seemed that perhaps transplantation was not meant to start at that time (15).

I felt I should work on transplantation research full-time instead of part-time in a busy clinical job. The chief surgeon under whom I worked warned the ward sister to keep an eye on me lest I fill the patients' beds with dogs, so although it was my hope to spend my career trying to combine science and surgery it was necessary to spend a period devoted entirely to research. I sought Medawar's advice on this and he suggested a number of centers in America. He knew I wished to be a clinician, and I felt that the Brigham was the best of his suggestions so I wrote to Drs. Moore and Murray. I was fortunate enough to be offered a post and obtained a Harkness Fellowship. My wife and I with our two young daughters sailed on the *Queen Elizabeth*. I remember playing squash inside the second funnel.

On arrival in New York I took the train to Tuckahoe to the Burroughs Wellcome Laboratories to meet George Hitchings and Trudy Elion with whom I had corresponded. I could not have been received with more friendliness by these two great scientists, recipients of the Nobel Prize in Medicine, 1989. They had synthesized purine and pyrimidine analogs designed especially for the treatment of cancer. In the hope of finding a compound with a better therapeutic index than 6-MP, they gave me a number of purine and pyrimidine analogs to investigate. With these in my briefcase, I arrived at the Brigham to be met by Dr. Murray - recipient of the 1990 Nobel Prize for Medicine - who was about to go on holiday. With typical American generosity, he offered me the use of his car and said he was delighted that I had come and that I could join their irradiation program. I was crestfallen since I had hoped to test the drugs that Hitchings and Elion had given me. I explained to Dr. Murray that I had come to work in his department hopefully to avoid the use of irradiation. He then apparently recalled the paper that I published in the *Lancet*; I had the impression that Dempster's letter was on his mind, and he said I could start with the drugs and if they did not work out I could join the irradiation program. I worked day and night operating and taking care of my animals. My wife helped me exercise and feed the dogs with excellent meals from the Brigham kitchen, better than we were able to afford for ourselves. Catching urine from the male dogs was easy, but from the females required intense observation and a rapid lunge to place the bowl on the grass in time. This

Roy et al. with Lollipop after grand rounds in 1960. Left to right, RYC, Trudy Elion, Jenze Hitdiys, man from Wellcome, Dited Aeger, Joseph Murray.

maneuver became known to my colleagues as the "Calne Crouch."

After his return from holiday, I was able to show Dr. Murray dogs with renal allografts treated with 6-MP who were doing well, and as soon as he saw them, he devoted a great deal of his time and enthusiasm to supporting this work. BW57-322, an analog of 6-MP, later known as azathioprine (Imuran), which seemed to be the best of these agents, was a little superior to 6-MP (16,17). The high point of these experiments was the presentation of the first "patient" to survive a renal allograft, treated with azathioprine and with normal renal function at six months, at Grand Rounds at the Peter Brent Brigham Hospital. After the case history had been read, the door was opened and my dog, Lollipop, pranced into the crowded auditorium, making friends with the distinguished Professors in the front row. Shortly after this, the use of thiopurines in clinical transplantation enabled the first phase of clinical organ transplantation to be established with moderate success.

After a wonderful 18 months in the United States, which included a 15,000 mile camping tour of North America, I returned to work as a senior registrar at St. Mary's Hospital where they had experience of kidney transplantation with x-irradiation. I suggested we should try azathioprine and steroids since the failure rate at St. Mary's with x-irradiation was 100 percent. Stan Peart, the Professor of Medicine, agreed, and with the help of Ken Porter we were able to start kidney grafting using azathioprine and steroids. I then moved to Westminster Hospital with Harold Ellis and continued the kidney transplant program. The theater sister would not permit cadavers in her operating rooms so we had to remove kidneys in the open wards. It must have been dreadful for the other patients in the large wards to see the surgeons go behind the curtains and operate on a corpse in bed, with blood trickling on the floor under the curtains.

In 1965 I moved to the Chair of Surgery at Cambridge where the prospect of renal transplantation was greeted with indifference or hostility by most of my new colleagues but was supported by a few. The program soon got under way and Dr. David Evans, a young nephrologist, joined me in the Department of Surgery, an act of professional suicide as judged by his colleagues. However, thanks to his superb efforts, dialysis and patient care reached a high standard. We developed close contact with Medawar's department with regular meetings, either in Cambridge or Northwick Park. Valery Joysey set up the Tissue Typing Laboratory in Cambridge.

The goal of transplantation surgery has always been to produce tolerance without causing harm by nonspecific immunosuppression. In 1959 at the Agricultural Research Station at Compton I had worked with naturally tolerant dizygotic cattle twins and confirmed Simonsen's observation that tolerance could be demonstrated with kidney grafts as well as with skin.

After the move to Cambridge I had no facilities for research, but thanks to the generosity of Richard Keynes, I was allowed to work at the Agricultural Research Station at Babraham. There I met Richard Binns who had just completed his thesis on the production of experimental tolerance in the pig by intrauterine embryo injection, a direct application of the Billingham, Brent, Medawar, and Sparrow experiment (18). The behavior of his tolerant animals to donor kidneys seemed an important subject and we found that kidneys were less likely to be rejected than skin from the same donor.

I had not, up until this time, been involved in experimental liver grafting, although Dr. Francis Moore had carried out experiments developing the technique in dogs at the Brigham when I was there. At about this time we heard of some liver grafting experiments performed in pigs by Terblanche in Bristol (19) and Garnier and Clot in Paris (20); some allografted pigs survived surprisingly long periods with their orthotopically grafted livers. This seemed to be of particular interest in view of the work that we had done in collaboration with Richard Binns. We set about developing the technique of orthotopic liver allografting in the pig. This required much perseverance in the face of many disappointments but eventually we showed that liver grafting could make the animal tolerant to other tissue from the same donor, the first demonstration of an operational tolerance in immunologically mature animals without the use of immunosuppressive agents (21). These findings were more elegantly demonstrated by my colleagues Zimmerman, Kamada, Davies, and Roser (22) in liver grafts between different rat strains.

Starzl did the first clinical liver transplantation in 1963 but the results were dismal (23). However, since we had now developed the technique and had some information on the immunology of liver grafting in the pig, I felt that the time had come to embark on a clinical program.

There was widespread opposition to this amongst my colleagues but a young adult with primary cancer of the liver was under my care and a child with mumps encephalitis was diagnosed as brain dead and his organs were offered for transplantation. Fortuitously on that day, Dr. Francis Moore was visiting his son who was a PhD student in molecular biology in Cambridge. He contacted me socially and when I told him of our possible liver graft, he came immediately to old Addenbrooke's Hospital. We gathered colleagues round in a circle and after the clinical presentation of the details of the potential recipient and donor I asked each in turn for his advice. They were unanimous in advising me against the liver transplant although each had a different reason. The last opinion I solicited was that of Dr. Moore, well known even in Cambridge. He said "Roy, you've got to do it." This took the meeting by storm and we left immediately for the operating theater. Dr. Moore was an enthusiastic first assistant for the first liver graft to be performed in Cambridge, which was technically successful (the patient survived six weeks but ultimately succumbed to a lung infection). Since that day in 1968 in a collaborative program with Dr. Roger Williams of Kings College Hospital in London, we have done approximately 900 liver grafts with steadily improving results. Many of the patients are children for whom donor organs are particularly scarce. The compassionate portrayal of the need for pediatric liver donation by Esther Rantzen and her colleagues in the television program "That's Life" convinced the public that cadaveric organ donation could be a gift of life.

We continued to search for better methods of immunosuppression with an aim to eventually producing tolerance. After we had followed many disappointing leads, in 1977 Jean Borel presented his experiments on the cyclic peptide cyclosporine A (CsA) to the British Society of Immunology (24). Dr. David White, an immunologist in my department, thought this compound might have antimacrophage activity and at that time we were interested in the macrophage. One of my visiting fellows, a Greek surgeon, Alkis Kostakis, spent nearly two years with us but had not been successful with his experiments. He told me that his Professor would be upset if he had not produced anything during his time in Cambridge and he said he wanted to study immunosuppression, so he learned how to transplant hearts heterotopically in rats and then started looking at conventional immunosuppressive drugs. Dr. White thought he might like to look at CsA and some two months later he came to me very excited explaining the wonderful results he had obtained with CsA in prolonging heart transplants in the rat (25,26). It seemed to be too good to be true and I thought he might have mixed up the

Delivering the original paper on Cyclosporine, Rome 1978.
First use in organ-grafted animals and man.

With a patient and her husband on the top of a Sivies Mountain. ca. 1980.

Receiving the Knighthood, Buckingham Palace, 1986.

rat strains, but on repetition, even better results were obtained with a Greek solvent for CsA when he received some olive oil from his mother who was worried that he might starve whilst he was in England.

I telephoned Sandoz and asked for some more CsA to study in large animals, and they told me they had stopped working with the compound but we could have some of what was left in their lab. We investigated CsA in dogs with kidney grafts and in pigs with orthotopic heart grafts (27,28). We found that it was far better than any other agent in both these models and proceeded to plan a pilot experiment for the use of CsA in man (29,30).

To our intense worry, the early experience demonstrated a completely unexpected side effect of the drug in man, that of nephrotoxicity, which had not been observed in any of the animal experiments. Nevertheless, CsA has made an important difference to the results of all organ grafting and has permitted, for the first time, successful transplantation of the heart with the lungs and enabled vascularized pancreas transplantation to develop as a useful therapy. There has also been one successful transplant of the small intestine together with a liver from London, Ontario (31), a result probably due in part to CsA and also possibly to the biological effect of the liver. CsA also enabled organ transplantation to be performed in children without severely stunting their growth or producing Cushing's Syndrome, which used to be such a sad side effect of the high steroid dose perviously necessary.

These are the highlights of my recollections. I have been exceedingly lucky in the positive results of some experiments. The clinical need has always been the underlying purpose in the research. Looking back, it is interesting to see how repeatedly the early ideas and efforts have been regarded by many as stupid, crazy, or dangerous and when they have fitted into the pattern of established therapy, they are perceived as obvious and the many struggles and disappointments are forgotten. In the face

Sailing in Spain, 1989.

R.Y.C. and a small girl with a liver graft, 1990.

of established successful therapy, opposing views of our conservative profession change to acceptance and the demand for more treatment. There are not enough organs available for those who need them. To satisfy that demand will raise many more serious ethical worries than in the past. As methods of controlling rejection improve, who should be given organs? How can we avoid commercial trade or even organized crime being involved in this shortage of the most valuable gift that can be offered to a patient? The only way in which this shortage could be solved would be to use organs taken from animals or by advances in an understanding of tissue differentiation and genetic engineering to grow organs in culture that will not be rejected. These developments will not take place unless animal experiments continue. As a form of research in developed societies, this is becoming increasingly difficult.

Organ transplantation has moved from the laboratory to the clinic as a result of the work of many scientists. My own endeavors have been particularly helped by Medawar and those colleagues mentioned above. Perhaps the greatest stimulus of all was to be told that it could not be done.

I will finish with a quotation from Lord Lister in his graduation address delivered in Edinburgh in 1876, "...and truly if we have nothing but pecuniary rewards and worldly honors to look to, our profession would not be one to be desired, but in fact you will find it is attended with peculiar privileges second to none in intense interest and pure pleasure."

Painting accepted (upper left) at Royal Academy Summer Exhibition, 1989.

Our family at the Lisler Medal oration, R.C.S., 1984.

Celebrating Nobel Prize for George and Trudi at V and A, 1989.

Operating at Addenbrooke's Hospital, 1990.

REFERENCES

1. Gibson T, Medawar PB. The state of skin homografts in man. J Anat 1943; 77:299.

2. Medawar PB. The behaviour and fate of skin autografts and skin homografts in rabbits. J Anat 1944; 78:176.

3. Medawar PB. A second study of the behaviour and date of skin homografts in rabbits. J Anat 1945; 79:175.

4. Simonsen M, Buemann J, Gammeltoft A, et al. Biological incompatibility in kidney transplantation in dogs. Experimental and morphological investigations. Acta Path Microbiol Scand 1953; 40:480.

5. Dempster WJ. Kidney homotransplantation. Br J Surg 1953; 40:477.

6. Hume DM, Merrill JP, Miller BR, et al. Experience with renal homotransplantation in the human: report of nine cases. J Clin Invest 1955; 34:327.

7. Murray JE, Merrill P, Harrison JH. Kidney transplantation between seven pairs of identical twins. Ann Surg 1958; 148:343.

8. Hamburger J, Vaysse J, Crosnier J, et al. Transplantatin d'un rein entre Jumeaux non monozygotes apres irradiation due Receveur. Bon functionnement au quatrieme mois. Note preliminaire. Presse Med 1959; 67:1771.

9. Murray JE, Merrill P, Harrison JH, et al. Successful homotransplantation of the kidney between nonidentical twins. N Engl J Med 1960; 262:1251.

10. Porter KE, Murray JE. Arch Surg 1958; 87:908.

11. Schwartz R, Damashek W. Drug induced immunologic tolerance. Nature 1959; 183:1682.

12. Calne RY. The rejection of renal homografts. Inhibition in dogs by 6-mercaptopurine. Lancet 1960; 1:417.

13. Dempster WJ. Rejection of renal homotransplants. Lancet 1960; 1:551.

14. Zukoski CF, Lee HM, Hume DM. The prolongation of functional survival of canine renal homograft by 6-mercaptopurine. Surgical Forum 1960; 11:470.

15. Hopewell J, Calne RY, Beswick I. Three clinical cases of renal transplantation. Brit Med J 1964; 1:411.

16. Calne RY. Inhibition of the rejection of renal homografts in dogs with purine analogues. Transplant Bull 1961; 28:445.

17. Calne RY, Murray JE. Inhibition of the rejection of renal homografts in dogs by Burroughs Wellcome 57-222. Surg Forum 1961; 12:118.

18. Billingham, Brent, Medwar PB, et al. Quantitative studies on tissue transplantation immunology: survival times of skin homografts exchanged between members of different inbred strains of mice. Proc R Soc B 1954; 143:43.

19. Terblanche J, et al. The use of the pig as an experimental animal for orthotopic liver transplantation. Br J Surg 1967; 54:231.

20. Garnier H, Clot JP, Bertrand M, et al. Biologie experimentale: Greffe de foie chez le Porc: Approche chirurgicale. C R Acad Sci (Paris) 1965; 260:5621.

21. Calne RY, Sells RA, Pena JR, et al. Induction of immunological tolerance by porcine liver allografts. Nature 1969; 223:5205.

22. Roser BJ, Kamada N, Zimmermann P, et al. Immunosuppressive effect of experimental liver allografts. In: Calne RY, Ed. Liver Transplantation. London and New York, Grune and Stratton Ltd, 1983; 35.

23. Starzl TE, Marchioro TL, VonKaulla KN, et al. Homotransplantation of the liver in humans. Surg Gynecol Obstet 1963; 117:659.

24. Borel JF, Feurer C, Magnee C, et al. Effects of the new antilymphocytic peptide Cyclosporin A in animals. Immunology 1977; 32:1017.

25. Kostakis AJ, White DJG, Calne RY. Prolongation of the rat heart allograft survival by Cyclosporin A. IRCS Med Soc 1977; 5:280.

26. Kostakis AJ, White DJG, Calne RY. Toxic effects in the use of Cyclosporin A in alcoholic solution as an immunosuppressant of rat heart allograft. IRCS Med Soc 1977; 5:243.

27. Calne RY, White DJG. Cyclosporin A - a powerful immunosuppressant in dogs with renal allografts. IRCS Med Soc 1977; 5:595.

28. Calne RY, White DJG, Rolles K, et al. Prolonged survival of pig orthotopic heart grafts treated with Cyclosporin A. Lancet 1978; 1:1183.

29. Calne RY, Rolles K, White DJG, et al. Cyclosporin A initially as the only immunosuppressant in 34 recipients of cadaveric organs: 32 kidneys, 2 pancreases, and 2 livers. Lancet 1979; 2:1033.

30. Calne RY, White DJG, Thiru S, et al. Cyclosporin A in patients receiving renal allografts from cadaver donors. Lancet 1978; 2:1323.

31. Grant D, Wall W, Mimeault R, et al. Successful small bowel/liver transplantation. Lancet 1989; 335:181.

CURRICULUM VITAE

Roy Yorke Calne

PERSONAL

Born:	December 30, 1930; Richmond, Surrey, England
1986	Knight Bachelor

EDUCATION

Lancing College and Guy's Hospital Medical School

POSITIONS

1953-54	House Physician, Surgeon and Thoracic House Surgeon, Guy's Hospital
1954-56	Royal Army Medical Corps, Served with 2nd Gurkhas Hong Kong and Malaysia
1957	Departmental Demonstrator, Department of Human Anatomy, Oxford
1957-58	Senior House Officer, Wingfield Morris Hospital, Oxford
1958-60	Surgical Registrar, Royal Free Hospital
1960-61	Surgical Research Fellow, Peter Bent Brigham Hospital Boston, Massachusetts, United States
1961-62	Lecturer in Surgery, St. Mary's Hospital, London
1962-65	Senior Lecturer and Consultant in Surgery, Westminster Hospital, London
1965-	Consultant Surgeon, Addenbrooke's Hospital, Cambridge
1965-	Professor of Surgery, University of Cambridge
1965-	Fellow of Trinity Hall, Cambridge
1987-89	Examiner in Surgery, Universities of Cambridge, Oxford, London, Edinburgh and Glasgow

PROFESSIONAL SOCIETIES

1983-84	Foundation President, European Society of Transplantation
	The Royal College of Surgeons 1977-90 Councillor 1987-89 Vice-President
	The Royal College of Surgeons Court of Examiners
1990-91	President Elect, The Transplantation Society

AWARDS

1952	Beaney Prize for Pathology, Guy's Hospital
1953	Distinction in Medicine, London MB
1957	Hallet Prize, Primary FRCS (Eng.)
1960	Legge Award for Research, Royal Free Hospital School of Medicine
1960	Harkness Fellowship of the Commonwealth Fund
1961	Jacksonian Prize, Royal College of Surgeons Dissertation on the subject of Tissue Transplantation

1962	Hunterian Professorship, Royal College of Surgeons, Lecture on Inhibition of the Rejection of Renal Homografts in Dogs by Drugs
1964	Cecil Joll Prize, Royal College of Surgeons for contribution to fundamental knowledge on renal transplantation and especially with regard to methods of suppression of the immune reaction
1969	Prix de la Societe Internationale de Chirurgie for contributions to liver transplantation
1972	Elected Fellow of the American Surgical Association
1973	Fellow of the Royal Society
1978	Faltin Medical, Helsinki for contributions to liver transplantation
1983	Mrs. Law-Lui Lecturer, Association of Surgeons of South East Asia
1984	Lister Medal of the Royal Society, The Royal Colleges of Surgeons of England and in Ireland and the Universities of Edingburgh and Glasgow
1986	M.D. (Hon Causa) University of Oslo
1987	Elected Fellow of the American College of Surgeons
1987	Galen Medal, Worshipful Society of Apothecaries of London
1989	Hunterian Oration, Royal College of Surgeons
1989	The Royal College of Physicians
1990	Elected Fellow of The Philippine College of Surgeons
1990	Cameron Prize of The University of Edinburgh
1990	M.D. (Hon Causa) University of Athens
1991	M.D. (Hon Causa) Hannover University

PUBLICATIONS

Total: 380 papers, 18 books

SUMMARY

Experimental and clinical research has been in the field of organ transplantation and immunosuppression. In 1959, the first successful experiments with the thiopurings as suppressors of renal allograft rejection in the dog were begun and published in the Lancet (1960) i, 417-418. This work continued in Boston (Transplant Bull(1961) 28, 445-461). Some ten years of work were devoted to the operational tolerance in orthotopic liver allografts induced in some pigs and certain rat strains across the major histocompatibility barrier. This phenomenon is still being studied and may have relevance to the reports of better survival of kidney grafts and intestinal transplants when a liver from the same donor has been grafted. The first experiments using Cyclosporin A in organ grafted animals and its application to man were in Cambridge University Department of Surgery where (Lancet 1979, ii, 1033-1036), to date, approximately 1208 kidneys and 900 livers and 45 pancreases have been transplanted in patients.

THE REESTABLISHMENT OF CADAVER KIDNEY TRANSPLANTATION: EARLY KIDNEY TRANSPLANTATION AT THE CLEVELAND CLINIC

Willem J. Kolff and Satoru Nakamoto

Address: Kolff's Laboratory
Department of Surgery
University of Utah
Dumke Building
Salt Lake City, Utah 84112

Willem J. Kolff and Satoru Nakamoto

(Left to right) Drs. Sat Nakamoto, W.J. Kolff, and Yuki Nosé in Cleveland, Ohio, around 1960. It was Dr. Nosé's idea to use a washing machine as the artificial kidney.

W.J. Kolff in 1985

THE REESTABLISHMENT OF CADAVER KIDNEY TRANSPLANTATION: EARLY KIDNEY TRANSPLANTATION AT THE CLEVELAND CLINIC

Willem J. Kolff and Satoru Nakamoto

In 1962, one of our residents visited the heads of the various departments of the Cleveland Clinic in Cleveland, Ohio, and suggested that the clinic should begin a kidney transplantation program. He got absolutely nowhere; he was told that it would not work, and if after many years it proved to work, that would be time enough for the Cleveland Clinic to get on the bandwagon.

In 1950, W. J. Kolff arrived at the Cleveland Clinic to join Dr. Irvine Page, a nationally recognized expert on hypertension. Kolff suggested that if he would treat the uremia in renal patients and Page would treat the hypertension, they might form a very strong team. However, it did not work out that way. Instead Kolff removed both kidneys of a number of unfortunate dogs and confirmed Arthur Grollman's observation that arterial hypertension can occur in animals without kidneys. He also found that this *renoprival* hypertension could be reduced to normal within a few hours if the renoprival dog was made to perfuse a pair of normal kidneys (1). In 1963 after doing bilateral nephrectomy in human patients and subsequent transplantation, we felt that further experiments in dogs were no longer necessary or justified.

In 1955, Kolff asked for and received permission to make a disposable artificial kidney; the twin-coil kidney was the result (2). Soon referral of patients with uremia grew, and we found ourselves in a very hopeless situation. The Cleveland Clinic would not allow us to maintain patients on chronic hemodialysis for fear that they would occupy too many beds. Yet these patients continued to come.

Dr. Eugene Poutasse was an excellent urological surgeon. One of his specialties was the treatment of Goldblatt-type hypertension. He cut a narrow section out of the renal artery and sewed the two ends together again. Thus, there was no doubt that he would be able to do a kidney transplantation. Poutasse approached me, and, knowing that the overall opinion of the Cleveland Clinic was against it, we decided to start six patients in rapid succession in the hope that we might have a survivor before the administration would catch on. We also decided we would bilaterally nephrectomize these patients first, making their hypertension easier to treat and hopefully prevent existing renal disease from being transferred to the transplanted kidney.

When the operating schedule was posted at the Cleveland Clinic Hospital, the Chairman of Surgery asked whether a committee would be appointed to decide whether bilateral nephrectomy was justified.

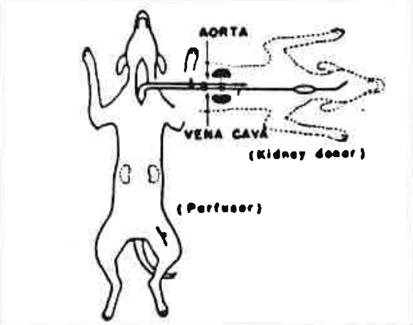
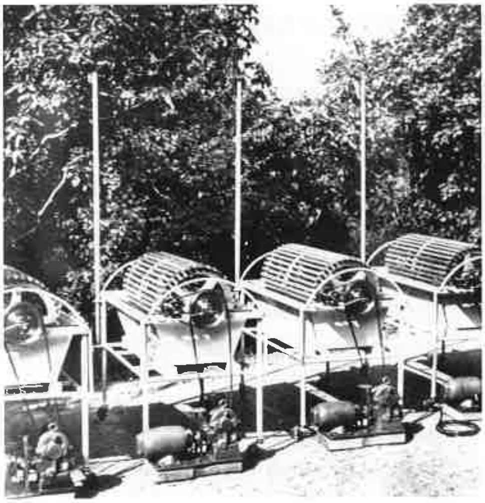


Figure 1. Kidney perfusion according to Brull. Blood flowed from the carotid artery of the perfusor to the lower part of the aorta and kidneys from another dog and returned via the vena cava and finally to the jugular vein of the perfusor. The dog furnishing the extra kidneys was removed when the circulation with the perfusor had become established. A pipette was used to measure flow in the vena cava.



An historical step in the development of artificial kidneys: the first rotating artificial kidney machines invented by Dr. W.J. Kolff in Kampen, the Netherlands, 1944.

The first patient whose life was saved by the artificial kidney. She was treated on September 11, 1945 in Kampen. The picture was taken approximately 4 weeks later.

Dr. Kolff driving a tractor on Kolff's farm in 1963 or 1964, pulling a trailer which carried 14 recipients of kidney transplants. All of them had been bilaterally nephrectomized before transplantation, half of them from cadaver kidney donors.

Dr. Poutasse answered that the chairman was removing both normal adrenals from patients for certain reasons without a committee at that time, and since the kidneys to be removed were shrunken, nut-sized, useless, and in cases of malignant hypertension even dangerous, we did not feel that a committee was necessary.

Kolff called John P. Merrill, who, more than anyone else, was responsible for the introduction of his rotating-drum artificial kidney in the United States (3). Merrill was extremely helpful. He discussed all the problems that might occur and gave us the most up-to-date doses of azathioprine (Imuran) and corticosteroid.

Since it was believed that perhaps multiple transfusions might sensitize patients and make them more likely to reject a transplant, he used peritoneal dialysis instead of artificial kidneys (which needed blood for priming) to treat uremic patients prior to kidney transplantation.

Merrill suggested that it might be interesting if we used artificial kidneys because perhaps the blood might make the recipient more tolerant (it turned out that our results were certainly no worse than those of Boston).

Our first patient was a 14-year-old girl with terminal uremia on the basis of contracted kidneys. On March 15, 1963, bilateral nephrectomy and thymectomy were done. The kidneys weighed 46 and 48 grams, were fibrosed, and partly calcified, probably on the basis of chronic pyelonephritis. On April 1, 1963, a renal homograft donated by her mother, was done. The immediate postoperative urinary output was from 150 to 200 ml per hour. The details of her history are presented in Figure 2 (4-6).

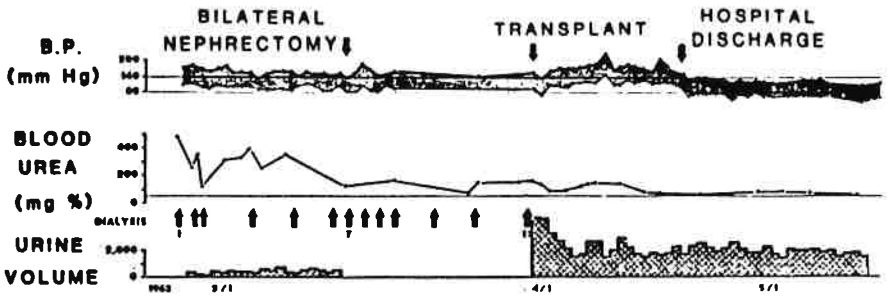
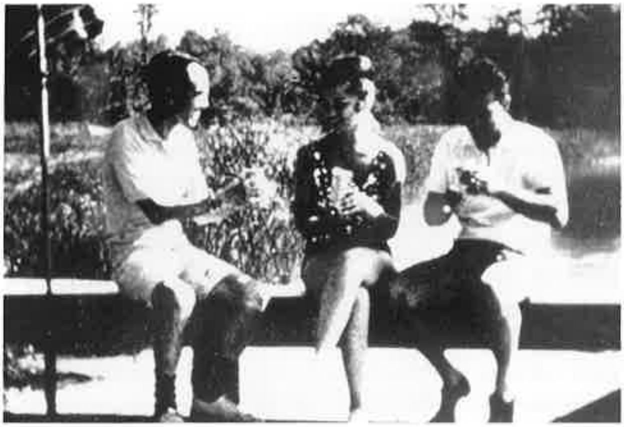
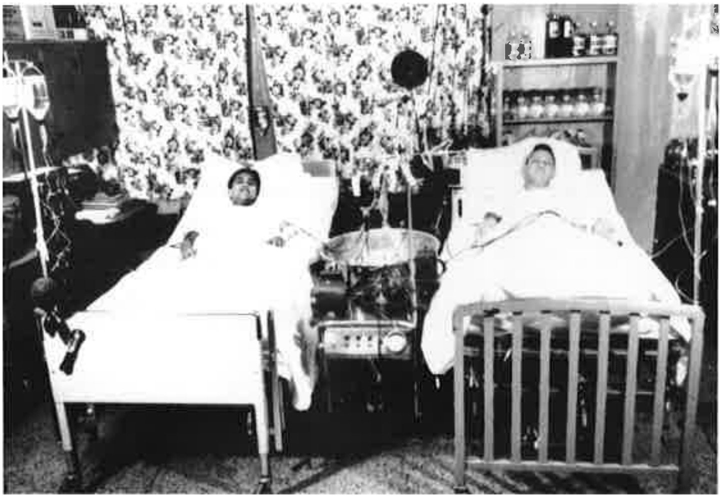


Figure 2. A 14-year-old girl with malignant hypertension of short duration, grade IV eyegrounds, blood urea over 400 mg per 100 cc, creatinine of 14 mg per 100 cc, a creatinine clearance of 1.4 cc per minute, cardiomegaly, pulmonary congestion, and pericardial friction rub. The diagnosis was chronic pyelonephritis with nephrocalcinosis. Multiple dialyses did not lead to control of the blood pressure or to improved eyegrounds, notwithstanding the use of drugs. Bilateral nephrectomy after the seventh dialysis was followed by more easily controlled blood pressure with eyeground improvement. Following transplantation of a kidney from her mother and some evidence of rejection, a rise in blood pressure necessitated the use of sodium nitroprusside and increased doses of corticosteroids and antimetabolites. A period followed in which the blood pressure was normal or near normal, sometimes even without the use of drugs. However, it rose again during a second rejection. This rejection and the rise in blood pressure were also overcome. Seven months after the transplant, she is slightly hypertensive, 140/90, with grade I eyegrounds.



Dr. Sat Nakamoto with transplant patients in 1946.

Twin-coil kidney made in 1955 by Kolff and Watschinger. Two patients can share the same bath.



Dietz van Dura, Dr. Erben, Dr. Yuki Nosé, and Dr. W.J. Kolff with washing machine artificial kidney around 1960.

The Saturday morning clinical conferences of the Cleveland Clinic were usually very good; they were well attended by the staff and by approximately 120 fellows who came from all parts of the world to be trained. The chairman of the morning conferences allowed Kolff to demonstrate the results of kidney transplantation. We were able to have five patients on the podium, all in apparent good health, all with a functioning transplant. Since all of them had been bilaterally nephrectomized, there was no question about the function. Complications and the problems of rejection were still to come. Those who had opposed us and started a movement to stop transplantation had no other choice than to offer congratulations.

A committee was formed, and for the first time it allowed dialysis of patients with chronic renal failure at the Cleveland Clinic, provided they were potential candidates for renal transplantation.

Dr. Gene Poutasse left the Cleveland Clinic and went to Norfolk, Virginia, but a very strong team of urologists under the leadership of Dr. Ralph Straffon took over. It included Clarence Hewitt, William Kiser, and Bruce Stewart. Dr. Satoru Nakamoto and Dr. Kolff had the help of very good residents, including George Dunea, Julio Figueroa, Masakatu Shibagaki, Dudley Seto, Fritz, Rosenbaum, Versaci, Khastagir, Brandon, Brown, and others. Many members of the staff participated in this work as is evidenced from their names appearing on various papers. Dr. Ray Gifford deserves special mention.

During the first night after a kidney transplantation, a resident would stay with the patient overnight and we used to say "if the patient dies, the resident will die too." Sometimes we saw massive diuresis - 10 liters or so, and it was difficult to maintain water and electrolyte balance.

In the following pages, we will tell of experiences and opinions on kidney transplantation at the Cleveland Clinic until 1967 when W. J. Kolff moved to Salt Lake City, Utah.

Figure 3 demonstrates how we followed our patients and recorded the doses of Imuran and Metacorten. The course of the same patient is described in more detail in the section on renal and renoprival hypertension. Note the large volume of urine immediately after transplantation (5,6).

In 1964, George Dunea from our group reported that there were 23 living patients who had received renal homografts at the Cleveland Clinic. Many of those patients were able to lead normal lives and some supported their families. Thirteen patients were working and two boys had returned to school (6).

Around this time, one of us visited Dr. Hamburger in Paris. Kolff had met Dr. Hamburger in 1946, right after the war, when he went to France to see whether or not there would be some interest in the artificial kidney. Dr. Hamburger was immediately interested and invited Kolff to his home. Hamburger became responsible for the French version of the rotating drum artificial kidney. When Kolff visited with him again in 1964, Hamburger was a delightful host and shared all his data and much of his enormous experience with us. He allowed Kolff to sit in at the weekly review of all his kidney patients. At that time they had to live inside greater Paris so that Hamburger could keep them under close control; and on that particular day, Dr. Hamburger had 20 patients alive with renal homografts. We had 21.

During that trip through Europe, W.J. Kolff showed a film which had been made on Kolff's farm which is 45 miles east of Cleveland, Ohio (video copies are available). They had invited all the patients to a summer party. The movie showed Kolff driving a tractor pulling a trailer carrying 14 recipients of kidney transplants. All of them had been bilaterally nephrectomized before transplantation - half of them with live kidney donors and the other half with cadaver kidney donors.

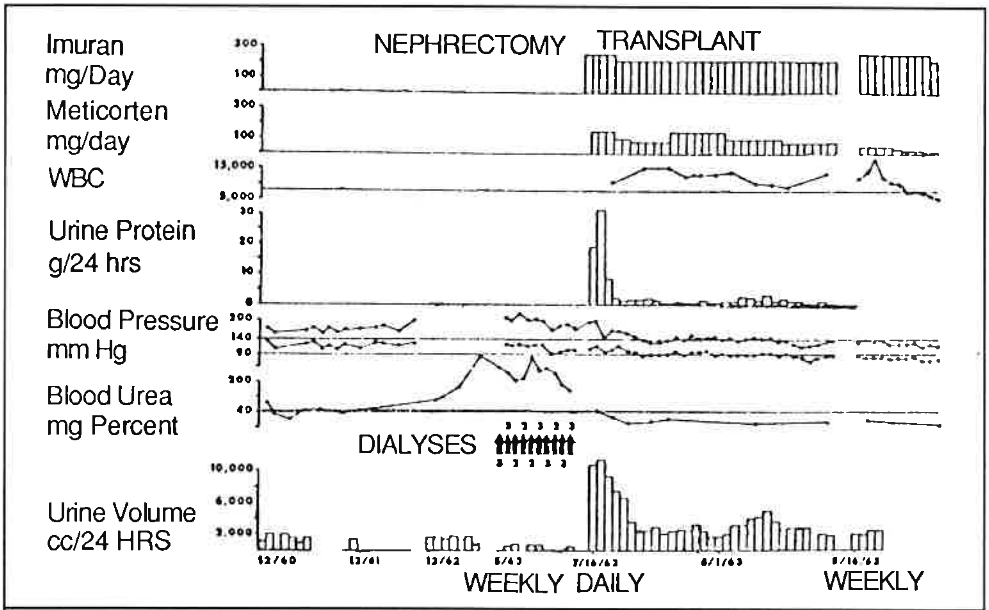


Figure 3. Case 4. Pertinent clinical and laboratory data. Note the gradual disappearance of hypertension. The proteinuria and urine output are not recorded at the end of the graph as the patient started to work and 24-hour daily collections of urine were discontinued. The numbers on the wide arrows represent the number of dialyses per week. The leukocyte count (WBC) is expressed per cubic millimeter (mm^3) of blood.

When Kolff showed this film in London, England, most of the audience thought that kidney transplantation was preposterous and came close to malpractice. He overheard some of the comments between two doctors sitting in the front row, saying "Look at them, the poor bastards." However, this changed rapidly when they saw the patients rowing in a boat, eating hot dogs, and having a really good time.

Around 1964, the following observations were made at the Cleveland Clinic:

Malignant renal hypertension can be treated better when both contracted kidneys are removed (6).

Renoprival hypertension is largely dependent on water and salt and becomes normotensive in dogs after perfusion of a normal kidney or in man after transplantation of a normal kidney (1,6).

Multiple transfusions beforehand do not prejudice transplantation results and may be beneficial.

Human cadaver kidneys can be used for transplantation. It is recommended that after the donor is pronounced dead, the circulation is maintained in open-heart cases with the heart-lung machine; in other cases, with closed-chest cardiac massage (9).

Acute tubular necrosis of a transplanted cadaveric kidney can recover in the recipient if he or she is adequately treated with hemodialysis.

Results of cadaver kidney transplantation were probably better than transplantation from unrelated live donors.

Bilateral nephrectomy of the recipient facilitates treatment after transplantation.

Scintigrams, angiograms, and renal biopsy of a nonfunctioning transplanted kidney are justified so that a dead transplant can be removed and then a second transplant can be done (10-12).

Cadaver Kidney Transplants

In 1968 we reviewed the world literature (13): "Kidneys from siblings or parents of a recipient are preferred as transplants. Of all renal homografts performed worldwide since January 1, 1965, approximately 63% of patients who received a transplant from a sibling, and 50% of those who received one from a parent have survived one year or longer."

"Transplantation of kidneys from unrelated donors has been less successful with 25% one-year survival of patients with transplants from living-unrelated donors, such as spouses, volunteers (prisoners), or obligatory nephrectomies. When the kidney was obtained from an unrelated cadaver donor, the one-year patient survival was 30%. If technical failures are excluded, that is kidneys that fail to function at all because of excessive length of time from death to transplantation, the results of cadaver kidney transplants approximate 48% one-year patient survival. At present, there is no definite explanation why kidneys from cadaver sources should survive longer than those form unrelated living donors.

"It is possible that the prolonged period of ischemia often associated with transplantation of the cadaver kidneys may in some way alter the antigenicity of the homograft or rather the antigens derived from the dead or half-dead cells of acute tubular necrosis have overwhelmed the immune mechanism of the recipient."

While the advantages of using cadaver donors for renal homografts were obvious, the poorer results obtained from this source of kidneys had discouraged use of cadaver donors in many medical centers. Our own experience allowed greater optimism.

Securing good cadaver donors required the close cooperation of all services within a hospital. When a patient is gravely ill, a member of the renal transplantation team is usually notified so that the suitability of the patient as a possible cadaver donor can be determined. In general, we have excluded potential donors with neoplasms, septicemia, known renal disease, and hypertension. If in doubt, we adopted the policy of surgical exposure to examine the kidneys when permission could be obtained.

We established the rule that when a cadaveric kidney was available, the urologist on call had to remove it. He could not second guess us if Kolff or Nakamoto believed that the kidney was OK, but that is where our power stopped. If the urologist did not like the look or smell or feel of that kidney, nobody could force him to implant it.

As of January 1966, simultaneous transplantations were performed on 18 occasions, the kidneys of a cadaver donor being used in two recipients. Occasionally a donor died in the operating room during an open-heart procedure, while still supported by the pump oxygenator. In these incidences, perfusion of the kidneys can be maintained until permission to use the kidneys can be sought and until a potential recipient is ready. When cadaver donors are used, the patient is pronounced dead by the primary attending physician of the donor and permission to use the kidneys for transplantation is also obtained in writing, from the nearest kin by his physician. Death is usually determined by cessation of electrocardiographic activity.

When the patient was pronounced dead, 200 mg of heparin and 500 ml of low molecular weight dextran were given intravenously. At the same time, a closed chest cardiac massage and artificial respiration using an endotracheal tube was started. The deceased patient was moved to the operating room where both kidneys were carefully removed under the usual sterile surgical conditions. We had a machine made by Jim Rand from an electric lawn mower that rhythmically compressed the heart. Cardiac massage could be maintained for 12 hours or so until the family was located.

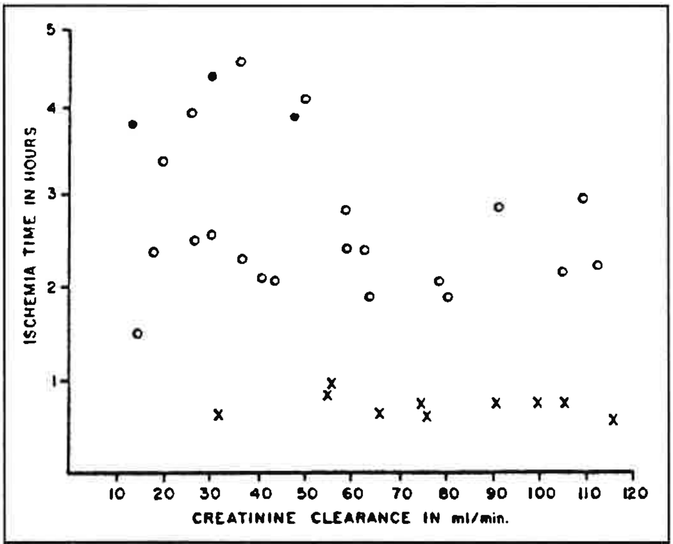


Figure 4. Kidneys from cadaver donors (○). Kidneys from cadaver donors in outside hospitals (●). Kidneys from live donors (X).

After the removal of the kidney, the renal artery was flushed with a warm perfusate until the afflux from the renal vein was clear. A cold perfusate was then used to cool the kidneys rapidly between 4°C and 10°C.

The kidney was stored in cold saline to maintain this temperature under thermocouple control. If a long-term period of ischemia was expected, the kidneys were placed in a hyperbaric chamber (a pressure cooker) at three atmospheres of oxygen (14).

Even in large hospitals, the source of suitable cadaver donors is limited. A program for securing donors from cooperating outlying hospitals was started. Six cadaver kidneys were secured in this manner, four of which functioned quite well despite the somewhat increased period of ischemia time (8,9,13) and later renal function, as shown in Figure 4.

We attempt to match major blood groups, but we have not considered this matching mandatory. Experience in renal transplantation seems to indicate that the incompatible combinations of AB to O, A to O, B to O, and B to A should be avoided.

We crossed this barrier on 11 occasions and saw no acute rejection on the operating table. However, only two patients of this group are still alive with functioning kidneys. We concluded that crossing the blood group barrier should be avoided whenever possible, but, for the time being, the patient with type O blood was considered a universal kidney donor and AB a universal recipient.

When the vascular anastomoses were completed, mannitol was infused into the recipient. When a live donor was used, urine appeared almost immediately, but its appearance may be delayed with cadaver donor kidneys because of the longer ischemic period.

It is impossible to make a prediction for the outlook for cadaver renal homografts (9) as to how long patients with a graft from a cadaver donor will survive. One patient survived 28 months before dying of a pulmonary embolus, and eight patients were alive for longer than a year. The most encouraging aspect of this problem is that most of those surviving more than three months were able to return to work and lead nearly normal lives.

Prolonged oliguria presents a problem in differential diagnosis. In most transplant recipients, oliguria was due to acute tubular necrosis, either already incurred in its dying donor or acquired secondary to the preoperative ischemia of the homograft kidney.

The production of urine within several minutes after a renal transplantation from a cadaver donor is the rule rather than the exception. Occasionally, the diuretic phase persists, and the patient recovers without

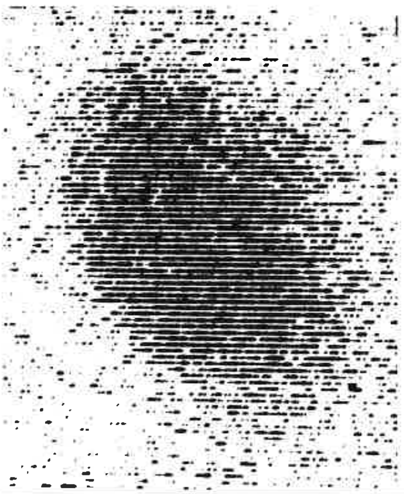


Figure 5. Renal scintigram obtained on the third postoperative day on a 42-year-old man who received a cadaver kidney transplant and was oliguric. Note the excellent uptake. The graft regained function.

the need for further dialysis. In most cases, however, oliguria develops and may last for as long as three or four weeks. It is during this initial period of oliguria that the need for an accurate diagnosis arises (10).

Is the kidney dead, or is it still alive? Is the allograft recoverable, or should it be removed? Is the ureter obstructed, or is the anuria due to thrombosis of the renal vessels? Our experience with the renal scintigram indicated that this is a valuable and harmless test in the evaluation of oliguria in the transplanted kidney (10).

The ^{203}Hg scintigram has been of value in assessing the viability of the homograft. If performed in the immediate postoperative period, an isotope uptake over the iliac fossa shows a patent vascular anastomosis. Unfortunately, further scintigrams are then not helpful because of the prolonged half life of ^{203}Hg. If the scintigram is made sometime during the 48- to 96-hour period after the onset of oliguria, it may be a more valuable test.

Absence of isotope uptake at this time usually indicates a nonviable kidney; however, it may be suppressed with acute tubular necrosis. Uptake should be good with ureteral obstruction, or urinary extravasation (Fig. 5).

Angiograms can further elucidate the situation. Angiograms of 20 renal homografts were obtained, 15 of which were kidneys from cadaver donors and five from live donors.

The iliac artery on the side of the homograft was selectively catheterized with a red Odman-Ledin catheter utilizing the Seldinger technique. Selective studies were performed in 17 of the 20 patients and have provided more information than is gained from common iliac artery and aortic injections (9).

When persistent arterial opacification was noted on delayed films, the corresponding renal vein was also selectively catheterized and studied (Fig. 6). In this series, nine angiograms were normal; three revealed renal artery thrombosis; one showed renal vein thrombosis; and seven

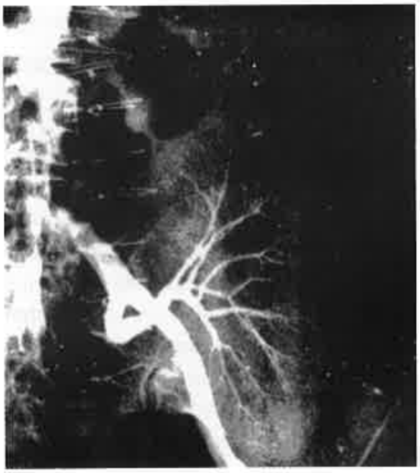


Figure 6. Renal angiogram taken on a 49-year-old woman after a poor scintigram. Although she was still oliguric the graft regained function. Note normal vascular pattern.

disclosed evidence of the rejection phenomenon. Of the nine patients with normal angiograms, five had viable transplants to date (range: 80 to 430 days) with essentially normal renal function. An angiogram did not always yield a visible pyelogram, so that obstruction could not be excluded (9,10).

Cystoscopy and retrograde pyelograms were required to investigate an obstruction as a cause of oliguria in a number of patients. Ureteral obstruction developed in only one patient and that was a later development.

In some patients, needle biopsy of the transplant was necessary to define the lesion causing the oliguria. This procedure was helpful in a number of instances, particularly when the oliguria was prolonged.

The diagnosis of rejection was often difficult to make from a renal biopsy but necrosis was readily apparent. The biopsy findings may be helpful in deciding whether a nephrectomy was required (15-17).

Second Renal Homograft

From January 1963 to June 1, 1966, 103 patients at the Cleveland Clinic received a total of 123 renal homografts (12).

Nineteen patients whose first renal homografts failed underwent retransplantation; one patient received a third homograft after the first two failed to function. As of July 1, 1966, eight of these patients were living, five with life-sustaining homografts that had been functioning for periods of 11 to 21 months. Three patients were maintained with periodic hemodialysis. Second renal homografts functioned in six of seven patients who lost their first homografts because of technical problems and four of these patients were alive with functioning homografts. Second renal homografts were rejected by five of the 10 patients who lost their first homografts because of rejection or thrombosis of the renal artery; only one of these patients was alive with a functioning homograft. We are reluctant to recommend retransplantation in patients who have rejected their first homograft, while we unhesitatingly recommend retransplantation in patients whose first homograft, though functioning, had to be removed because of technical problems.

The ureter was usually anastomosed directly into the bladder by a submucosal tunneling technique when distal ureteral blood supply appeared adequate. This was done because the overall incidence of leakage has been much less with ureteroneocystostomy than with primary ureteroureterostomy. If a leak developed later, the patient's own ureter was still available for ureteroureterostomy in the hope of saving the kidney.

When it became apparent that the first graft failed and the kidney could not be saved, the homograft was removed through the original incision in the lower part of the abdomen. Prompt removal of such a kidney can prevent infection in the graft site, and afford the patient a much better chance for rapid rehabilitation and preparation for a second transplant. The stump of the renal vein was simply ligated and left in situ; there has been no difficulty with subsequent necrosis, infection, or hemorrhage. The renal artery and ureter were removed completely; the patient's hypogastric artery was ligated with silk, and the bladder defect was closed in layers with catgut sutures.

Effect of Multiple Blood Transfusions

It has been debated whether or not multiple blood transfusions precipitate a superacute rejection of a transplanted homologous kidney. The chances of introducing more antigens to the recipient similar to the donor antigens, might increase with the number of transfusions. We reviewed the effect of multiple blood transfusions prior to transplantation in the first six patients. The only patient in a series of six in 1964 in whom the homograft failed, received a total of 115 hemodialyses prior to transplantation. The course of events following transplantation could be explained on the basis of hypotension during operation with reduced blood flow, etc. The other five patients received from six to 26 hemodialyses prior to transplantation; at least two units of blood were used per dialysis. There seemed to be no correlation in this group of five patients between the number of dialyses and the incidence of rejection reactions. The patients who received the greatest number of dialyses (excluding Case 6) had no evidence of rejection. No conclusive evidence for or against multiple transfusions was obtained. We believe that much later a study from Montreal indicated a favorable effect of multiple transfusions.

Renal and Renoprival Hypertension

Renal hypertension may be considered to have two components - renal and renoprival (Fig. 7) (5). When the renal component is dominant, the management of hypertension with salt and water restriction is more difficult. Bilateral nephrectomy removes the renal component and results in a renoprival hypertension, which is much easier to control. The successful transplantation of a kidney, in most instances, will convert the renoprival hypertension to normotension (18).

The renin content of some of the kidneys removed by bilateral nephrectomy has been studied by Haas and Goldblatt in 1959. The highest renin content was found in patients with the most severe hypertension and in whom there was notable regression of the hypertension after bilateral nephrectomy. In several patients who had hypertension that was easy to control with salt and water restriction, the kidneys contained small amounts of renin. In these patients, bilateral nephrectomy made little change in the degree of hypertension (6).

Hypertension

In patients who have had successful renal transplantations, hypertension has sometimes been a problem in the immediate posttransplantation period, but later has subsided. Hypertension that develops later may be a manifestation of rejection due to the development of a vascular lesion. The lesions described by Porter and associates in 1963 consisted of severe intimal thickening, producing partial occlusion.

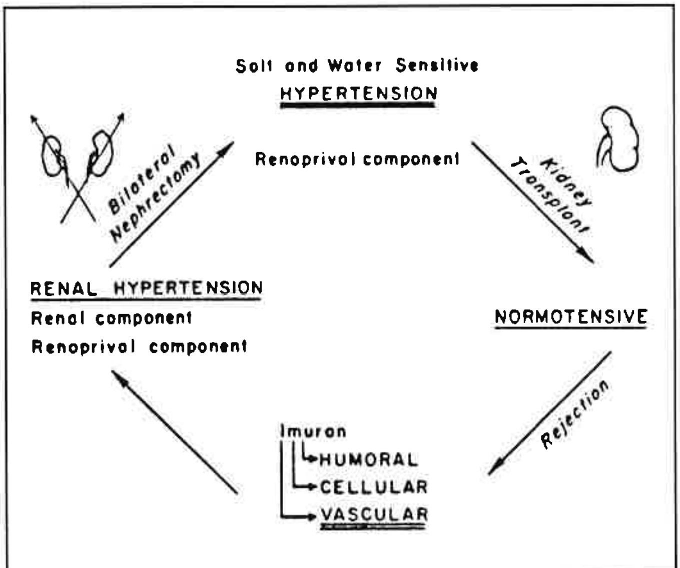


Figure 7. Diagram of renal hypertension following bilateral nephrectomy, kidney transplant, and rejection. Imuran and other drugs were used in an attempt to suppress the rejection.

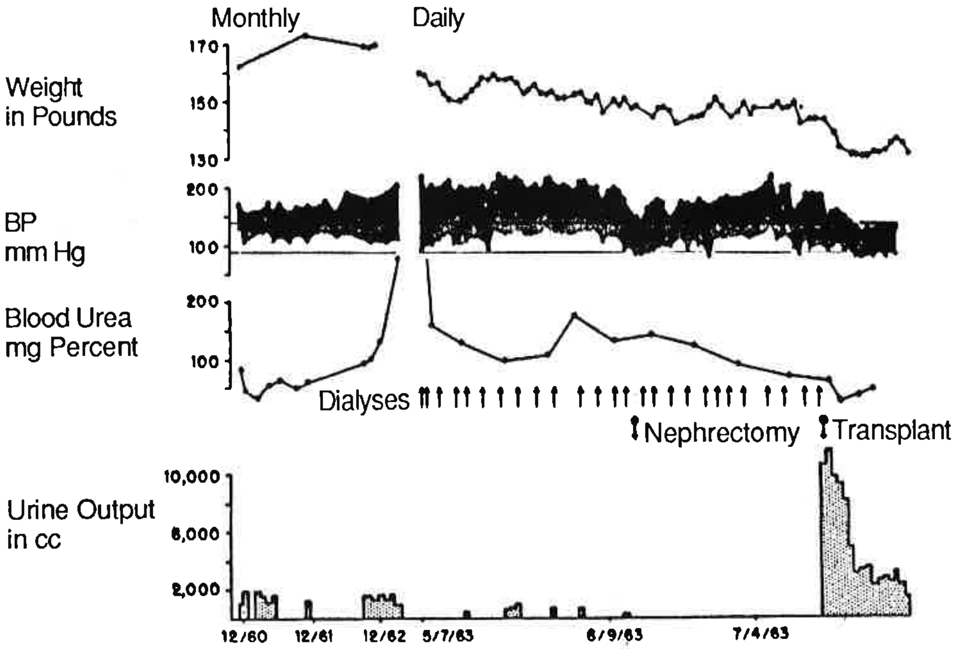
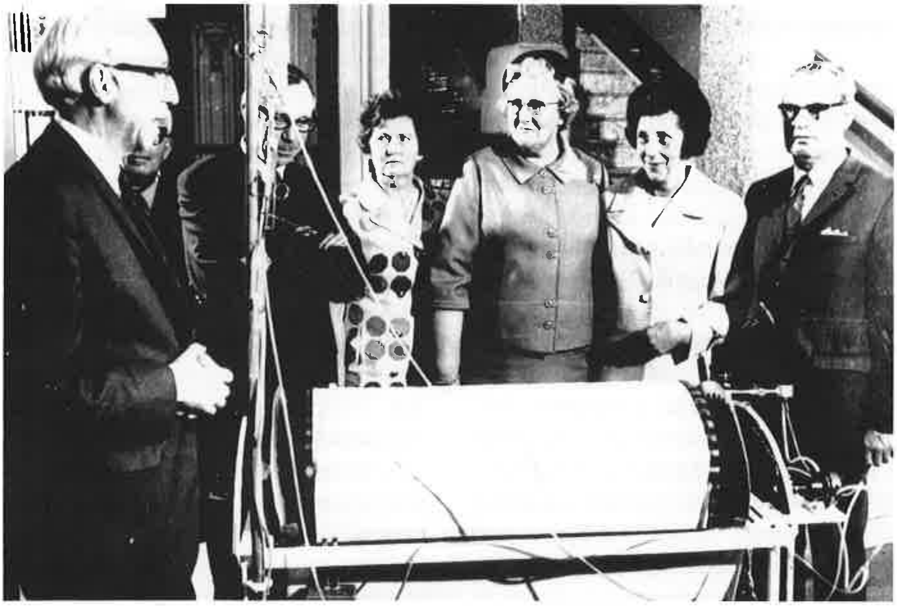


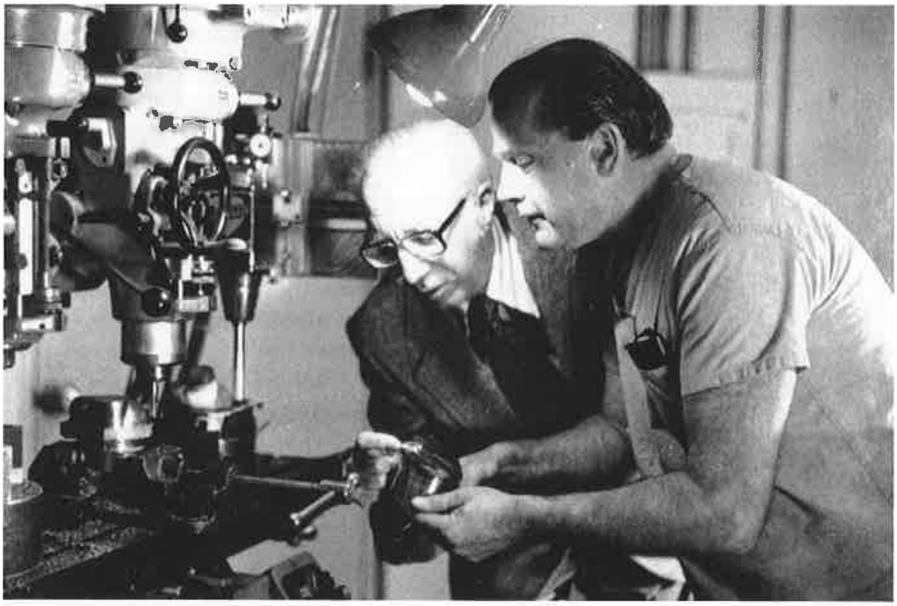
Figure 8. A 31-year-old traveling salesman with known hypertension since 1958, which became gradually more severe in December 1962, had blood pressure of 170/130 with grade IV eyeground changes. His uremia rapidly progressed. On May 7, 1963, hemodialyses were started, and immediate improvement of his general well-being resulted, although blood pressure was little affected. After bilateral nephrectomy the blood pressure became easier to manage. When the patient's weight began to increase, indicating some overhydration, both systolic and diastolic pressure became higher. After the twenty-sixth dialysis on July 16, 1963, a renal homograft from his brother was performed. Following massive diuresis the blood pressure rapidly fell to normal values. At the present time, November 1, 1963, the blood pressure has remained within normal limits without use of antipressor drugs. He has returned to work almost four months after transplantation. Eyeground changes can be classified as grade 1 or II.

In 1964, George Dunea described renal vascular changes seen in six patients after renal homotransplantation and pointed out their devastating effect. It was believed that these lesions were caused by an immunological process and antigen antibody complexes, thus we were lead to use larger doses of immunosuppressive drugs, especially prednisone and actinomycin C.

"Since November 1963, we have not seen vascular changes in the renal biopsies or necropsy material of further patients. We hope that the vascular process involved in the destruction of renal homografts, both in the acute and in chronic stage, may be arrested or perhaps even reversed with vigorous and continuous immunosuppressive therapy." (16, Fig. 8)



Dr. W.J. Kolff in 1970 when he became Honorary Citizen of the City of Kempen. Reunion with former head nurses.



Dr. W.J. Kolff working in his laboratory with Walter Rohloff. They are discussing metal mold for artificial heart.

Problems in the Selection of Recipients for Kidney Transplants

The enormous number of patients with terminal renal insufficiency requires that some selection be made before admitting the patient to a transplant program. The medical requirements are straightforward. There must be terminal renal insufficiency that is irreversible, requiring hemodialysis to maintain life (13). As defined by David Hume and coworkers, the ideal recipient for a renal transplant should have no serious infection, no generalized irreversible systemic disease, no abnormality of the lower urinary tract, and no serious emotional instability. Preferably, the patient should be less than 50 years of age, intelligent, and potentially capable of living a productive life. In many instances, it is nearly impossible to establish these criteria before or during the period of dialysis, since the state of illness often severely alters the patient's personality.

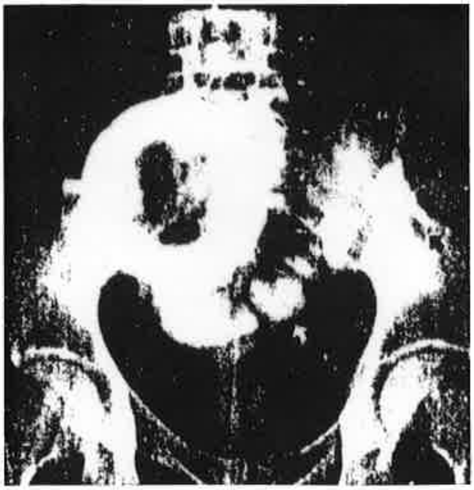


Figure 9. Intravenous urogram showing cadaver kidney transplant in left iliac fossa and uretero-ileal urinary diversion. Renal function has been excellent with average blood urea 30 mg/100ml and creatinine clearance 75 ml/minute.

In our experience, the vascular, cardiac, and neurologic changes incident to the renal failure were not necessarily disqualifying. Often astonishing improvement was achieved in a patient whose physical condition was such that the possibility of restoration of normal health appeared to be extremely remote.

"The remarkable recovery after kidney transplantation of a young girl who was dying from kidney failure emphasizes the difficulty in predicting the ultimate outcome based on the clinical status of the patient at the time organ replacement is contemplated.

"A congenital neurogenic bladder had predisposed this 13-year-old girl to chronic urinary tract infection. Recurrent pyelonephritis occurred, resulting in progressive renal failure. Despite numerous surgical attempts to rehabilitate the lower urinary tract, all efforts failed and renal function deteriorated. Her clinical condition became grave and she was near death from uremia. She was comatose and experiencing repeated seizures from hypertensive encephalopathy. Hemodialysis was utilized to prolong life. Her infected, nonfunctioning kidneys were removed, and at the time, a segment of the ileum was isolated to serve as a conduit for future urinary diversion. A cadaveric renal transplant with uretero-ileal urinary diversion was performed in February, 1965. Two and one-half years later, this attractive high school student continued to enjoy excellent health with normal renal function" (Fig. 9) (13).

Can You Deny Treatment?

Because of recent successes with chronic renal dialysis and transplantation, the problem now facing selection committees for renal transplantation is whether physicians can morally or ethically deny patients with terminal renal failure the hope of prolongation of life by these therapeutic means.

At present, all patients who might benefit from transplantation cannot be accepted, principally because of a lack of adequate dialysis and transplant facilities and difficulties in obtaining kidney donors. The financial and logistic problems related to large-scale dialysis or organ transplant programs are such that support by various governmental agencies will be required if all deserving persons are to be provided with such costly, complicated medical care in the future.

In our opinion, the most equitable selection of patients for renal transplantation at present appears to be on a "first come, first transplanted" basis, with selection limited to a medical triage to rule out other diseases that would prevent successful outcome. We have found that the responsibility for selection of recipients for organ transplantation may be conveniently delegated to a small committee of physicians within the institute.

William Kiser and Kolff wrote the above opinion in 1967. Six years later (1973), Public Law #92-603 recognized end-stage renal disease as a financial catastrophic disease and everybody covered by Social Security in the United States could claim 80 percent of all medical expenses with no questions asked about his or her personal finances.

Comparison of Kidney Transplantation and Dialysis

In September 1966, Drs. Kolff and Nakamoto gave a report in Amsterdam. "Transplantation of 125 kidneys, with 96 from human cadavers, and experience with more than 12,000 dialyses and six types of artificial kidneys form the basis of this study. Cadaver kidneys have often suffered when their previous owner died. Also, they have often been subjected to a period of ischemia. After transplantation, the majority of these kidneys recover like other kidneys recovering from acute tubular necrosis, but the recipient must be treated with dialysis (17).

"An example of this is a man in chronic renal failure who developed a rapidly

Table 1. Kidney transplants compared with dialysis.

	Cadaver Kidney Transplantation	Artifical Kidney
Initial mortality (morbidity) (or morbidity and mortality)	Loss of transplanted kidney 44=45% in 3 months, but patient may survive it.	Little mortality. High morbidity.
Life expectancy	Chronic rejection may still occur after 2 years or later. Uncertainty. Late vascular changes.	Metabolic diseases. Diseases appearing 2-6 years after onset of dialysis. Hazard of mishaps.
Well-being in successful cases	100%	75% of normal.
Hypertension	Cured	Difficult to manage at best.
Anemia	Cured	Difficult to manage at best.
Uremic neuropathy	Arrested. Functional improvement	Difficult to manage at best
Skin complications	Cured	Itch, urticaria.
Diet	None	High caloric, low protein, salt free.
Drugs	Immunosuppressive drugs.	Antihypertensive drugs.
Danger of infection	Yes, including virus and fungus.	Infection of shunt.
Life and activities	Unrestricted.	Restricted.
Infectious hepatitis	Occurs.	Occurs.

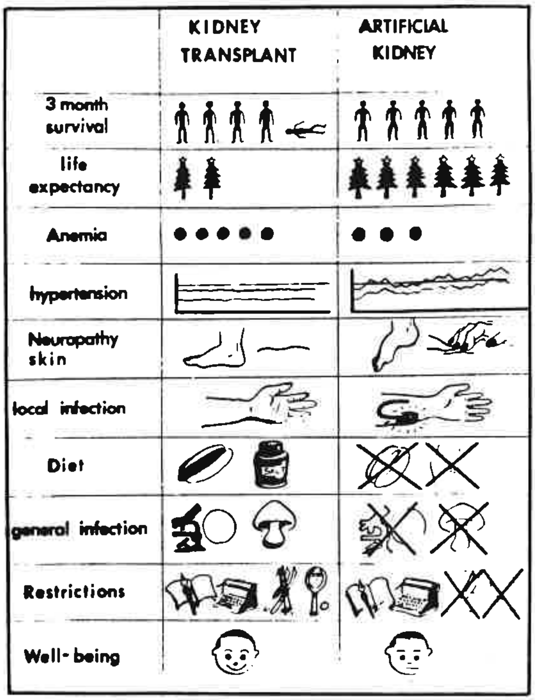


Figure 10. A schematic comparison made in 1967 of kidney transplantation and periodic hemodialysis in the therapy of chronic renal failure. The face in the lower level indicates that the picture was made by Dr. Yuki Nose.

progressing polyneuropathy. Neither more frequent dialysis nor anything else we tried could arrest its progression. Finally, we found a cadaver kidney for him. It took 25 days before it began to produce significant amounts of urine. The paralysis of most of the muscles of his arms and legs gradually improved. After 12 months, the blood creatinine was 1.2 mg percent.

"In short, this patient could not be maintained with dialysis because of progressive neuropathy. He was far better off with a relatively poor cadaver kidney."

Table 1 compares the results as we saw them in 96 patients with cadaver kidney transplants compared with life on dialysis (19).

In 1967, 500 kidney transplantations were done in the United States, so it offered a solution for only a few. Bankruptcy threatened anyone who had to pay for hemodialysis in the hospital, and we pleaded for the institution of home dialysis as a less expensive solution (13,19).

The schematic diagram (Fig. 10) compares the possibilities of treatment and examines the factors bearing upon the choices between transplantation and the artificial kidney:

The chance of survival for the first three months undoubtedly is better for patients treated with the artificial kidney than for patients receiving kidney transplantation. However, the life of dialysis patients is complicated by restriction with regard to food and activities, while shunt infection, anemia, progressive neuropathy, and hypertension present serious difficulties for some patients. In contrast, when renal transplantation is successful, the patient leads a relatively unrestricted life and enjoys a sense of healthy well-being, although generalized infection with bacteria, fungus, or virus looms because of immunosuppressive drugs (13).

In 1967, we believed that advances in both organ transplantation and periodic dialysis could lead to the situation where, by 1970, the patients with chronic renal failure could be completely rehabilitated by either method of treatment as depicted in Figure 11. Development of methods for assuring histocompatibility and new immunosuppressive agents could result in prolonged survival of grafts. Improved techniques for organ preservation (14) and storage would result in improved homograft function and would allow time for better donor-recipient matching and transplantation of the grafts to

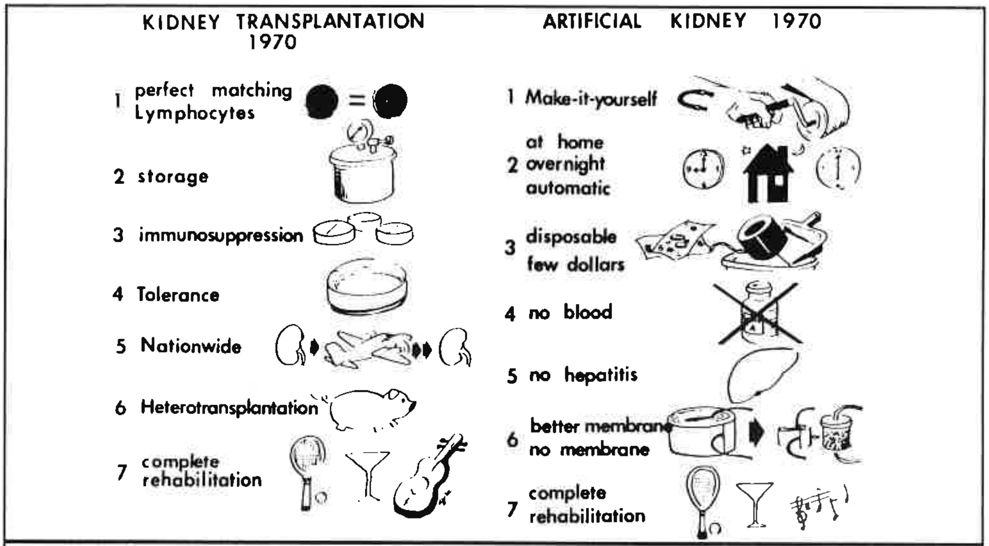

KIDNEY TRANSPLANTATION 1970
1 perfect matching Lymphocytes
2 storage
3 immunosuppression
4 Tolerance
5 Nationwide
6 Heterotransplantation
7 complete rehabilitation
ARTIFICIAL KIDNEY 1970
1 Make-it-yourself
2 at home overnight automatic
3 disposable few dollars
4 no blood
5 no hepatitis
6 better membrane no membrane
7 complete rehabilitation

Figure 11. A prediction of the advances to be made by 1970 in kidney transplantation and periodic hemodialysis in the therapy of chronic renal failure.

the most suitable recipients. The use of heterografts may become practical in the future, with development of improved methods for combatting rejection crises.

On the other hand, the perfection of compact, economical, simple dialysis units would allow the patient to perform self-dialysis at home during evening hours, thus not interfering with his usual daily occupation (13).

No membranes hinted at sorption artificial kidneys with activated charcoal, resins, and colloids. Persons who are suitable subjects for transplantation or who do not have a suitable kidney available for this purpose could thereby receive satisfactory treatment for an otherwise fatal condition.

We were too optimistic as far as time is concerned, but it takes optimists to bring progress in medicine.

Dr. W.J. Kolff with Nanette Adams. Nanette is a delightful young woman on dialysis since age 15. She has had several kidney transplants, has a healthy young son, is now back on dialysis.

REFERENCES

1. Kolff WJ. Hypertension: reducing function of the kidney. Cleveland Clinic Quarterly 1957; 24(3):141.

2. Kolff WJ, Watschinger B. Further development of a coil kidney. J Lab Clin Med 1956; 47(6):959.

3. Kolff WJ. First clinical experience with the artificial kidney. Ann Int Med 1965; 62(3):608.

4. Figueroa JE, Nakamoto S, Poutasse EF, Kolff WJ. Renal homotransplantation in man - report of six consecutive cases. Ann Int Med 1964; 51(2):88.

5. Kolff WJ, Nakamoto S, Poutasse EF, et al. Effect of bilateral nephrectomy and kidney transplantation on hypertension in man. Supplement II to Circulation, 1964; 29 and 30:1123.

6. Dunea G, Nakamoto S, Straffon R, Kolff WJ. Kidney transplantation - 1964. Arch Int Med 1965; 116.

7. Kolff WJ. Medical travelogue: about artificial organs, kidney transplantation & unrelated medical experiences in Europe. Ohio State Med J 1966; 62(4):325.

8. Straffon R, Hewitt CB, Kiser WS, et al. Clinical experience with the use of 79 kidneys from cadavers for transplantation. Surg Gynecol Obstet 1966; 123:483.

9. Figueroa JE, Rodriguez-Antunez A, Nakamoto S, Kolff WJ. The scintigram after renal transplantation in man. N Engl J Med 1965; 273:1495.

10. Alfidi RJ, Meaney TF, Buonocore E, Nakamoto S. Evaluation of renal homotransplantation by selective angiography. Radiology 1966; 87(6):1099.

11. Gifford RW, Deodar SD, Stewart BH, et al. Retransplantation after failure of first renal homografts. JAMA 1967; 199(11):799.

12. Kiser WS, Kolff WJ. When is transplantation of organs feasible or practical? In: Dowling HF, Ed. Disease-A-Month. Year Book Medical Publishers, Inc, 1967; 32.

13. Nakamoto S, Straffon RA, Kolff WJ. Three years' clinical experience with kidney transplantation. In: Brest AN, Moyer J, Eds. Renal Failure. J.B. Lippincott, 1967; 233.

14. Khastagir BK, Hino K, Kolff WJ. Experimental preservation of sheep kidney for transplantation. Cleve Clin Q 1968; 35:49.

15. Dunea G, Hazard JB, Kolff WJ. Vascular changes in renal homografts. JAMA 1964; 190:199.

16. Khastagir B, Montandon A, Nakamoto S, Kolff WJ. Early and late failures of human cadaveric renal allografts. Arch Intern Med, 1969; 123:8.

17. Straffon RA, Nakamoto S, Kolff WJ. Clinical experience with renal transplantation. Br Urol 1965; 47(4):370.

18. Kolff WJ, Nakamoto S. Cadaver kidney transplantation versus dialysis proc. 9th Int Cong Int Med, 1966; Excerpta Medica International. Congress Series, No. 121:122.

19. Kolff WJ. Kidney transplant or home dialysis? Postgrad Med J Appl Med 1968; 44(2):93.

CURRICULUM VITAE

Willem J. Kolff

PERSONAL

Born: February 14, 1911; The Netherlands
Marital Status: Married, 5 children
Citizenship: United States (1956): moved to United States in 1950

EDUCATION

1938	University of Leiden Medical School, Holland, M.D.
1946	University of Groningen, Holland (Summa Cum Laude) Ph. D.

POSITIONS

1967-86	Director of Institute for Biomedical Engineering
1967-86	Director of Division of Artificial Organs, University of Utah, Salt Lake City, Utah
1982-	Distinguished Professor of Medicine and Surgery, Research Professor of Engineering and Director of W.J. Kolff's Laboratory, Department of Surgery, University of Utah, Salt Lake City, Utah

AWARDS

	Total: 101 National and International Awards
	Commandeur in the de Orde of Oranje-Nassau
	12 Honorary Doctorates
1964	Cameron Prize of the University of Edinburgh, Scotland
1972	The Harvey Prize from Technion
1974	Orden de mayo al Merito en el Grado de Gran Official, the highest civilian award from the Argentine Government
1986	The Japan Prize
1990	Counted as one of the "100 Most Important Americans of the Century" in the special Fall issue of Life Magazine

PUBLICATIONS

Total: more than 600 publications including 5 books, 29 chapters in books, 6 forwards in books.

SHORT SUMMARY OF DR. KOLFF'S AND HIS COWORKERS' WORK

Dr. W.J. Kolff invented an artificial kidney in the Netherlands, of which he published in Acta Medica Scandivanica in 1944, while he was working in a small hospital in Kampen, the Netherlands. After World War II, he sent artficial kidneys to other places - New York, Montreal, London, etc. to prove that other than the Dutch could also be treated with dialysis. Today, a quarter of a million people are treated with hemodialysis.

Dr. Kolff moved to the United States in 1950 to devote himself mainly to the development of artificial organs. A twin-coil artificial kidney developed in 1956 was the first disposable artficial kidney and made dialysis possible all over the world.

A heart-lung machine on which Dr. Kolff started work in 1949 in the Netherlands was brought to clinical use in 1956. It was the first clinically used membrane oxygenator and led to the first consistently successful use of elective cardiac arrest in open-heart surgery.

Of the cardiac assist devices, the so-called intra-aortic balloon pump developed in Dr. Kolff's laboratory in 1961, together with Dr. Spyros Moulopoulos and Steve Topaz, is now the most popular cardiac assist device. An estimated 200,000 patients are treated with the balloon pump per year in the United States alone.

Work to develop better artificial hearts is still in progress. Success with the longest surviving animal (268 days) in Dr. Kolff's laboratory in 1981, led to the first human recipient of a permanent artificial heart - Dr. Barney Clark who lived for 112 days. Although he had many complications, mostly not related to the artificial heart, Dr. Clark retained his considerable sense of humor, his zest for life, his desire to serve mankind, and his love for his wife and family.

Presently, the air-driven artificial heart is mainly used as a bridge to donor heart tranplantation, if a donor cannot immediately be found. Just as an example, in 1986, of the 36 deathly ill recipients of the articial heart, 21 left the hospital with a functioning donor heart. A total of 100 people have received artificial hearts today.

Ultimately, 35,000 to 50,000 people will need cardiac replacements per year in the United States. With only 2,000 possible donor hearts available, there are 33,000 people who could be saved with artificial hearts.

W.J. Kolff believes the artificial heart will soon surpass the artificial kidney in the number of patients being treated. He believes an enjoyable existence will be possible for people now doomed to die, even if it means that the artificial heart implanted in the chest is tethered with short drive lines to a portable system. However, he has great hope for the "Clamshell-Electro-Hydraulic" artificial heart which is totally implantable (1990).

The feasibility of the artificial eye was proven together with Dr. William Dobelle by direct stimulation of the visual cortex of the brain.

The artificial ear developed with Dr. Donald Eddington uses another principle. It stimulates (as was done earlier by the House brothers) the acoustic nerve in the cochlea. One-third of the totally deaf people provided with the Utah artificial ear can have a telephone conversation.

The artificial arm developed by Dr. Stephen Jacobsen is sensitive enough to peel an orange but strong enough to crack a nut.

The main aim of Dr. Kolff's endeavors has been, and still is, to restore people to an enjoyable existence. If it is not enjoyable, it should not be done.

RECOLLECTIONS

H.M. Lee

Address: Medical College of Virginia
Department of Surgery
1200 East Broad Street
Richmond, Virginia 23298

H. M. Lee

Early

1983

1990

RECOLLECTIONS

H. M. Lee

My recollection of the early days of transplantation begins with Dr. David M. Hume and his arrival in Richmond in 1956 as Chief of the Surgical Department. Reportedly, his name was recommended by Dr. Hartwell Harrison, a urologist at Brigham Hospital who was involved in the early days of kidney transplantation with Dr. Hume. Dr. Harrison was a Virginian and had a cousin who was a faculty member of the surgical department in Richmond. I was a junior resident in surgical training at the time and did not know much about what was happening then. Dr. Hume immediately undertook the task of redesigning the surgical department, modeling it after Boston as a modern academic surgical department. In 1959, after my interview with Dr. Hume, I was placed in the surgical research laboratory as a research fellow before resuming clinical training. Looking back, Dr. Hume was trying me out to see whether I should be given the chance to resume clinical training in this new academic center since I was one of those risky foreign graduates. I was placed under the supervision of Dr. Charles Zukoski, then senior fellow in the research laboratory.

It was the "heyday" of the radiation biology atomic energy explosion. The surgical research activities were housed in the old research building called the Brown Sequard building, after the famous physiologist and was leaning slightly because it was built on the end of the street which was facing the valley. Obviously, the foundation was already slipping toward low ground. It housed a one million volt radiation machine which was used to radiate animals. One of the projects was to modify the antigens, namely the donor, and recipient in the transplant project. All of the projects were to radiate the animal with total body radiation and then reconstitute with fetal hemopoietic tissues, such as the liver and spleen, and transplant the kidney into the modified recipient (1).

Part of the project that I was assigned, along with Dr. Zukoski, was to screen the immunosuppressive agent in dog/kidney transplant experiments. We found that 6-MP was most effective in prolonging kidney transplant survival in the dog and we presented this at the Surgical Forum of the American College of Surgeons meeting in 1960. I found out later that this was one of the earliest papers proving chemo-therapeutic agents as an effective immunosuppressive drug. We learned also that Professor Roy Calne, then the research fellow visiting Brigham Hospital, confirmed the same effectiveness independently from us. My acquaintance with Sir Roy dates back to this period (2).

Dr. Monaco with Dr. Zukoski.

Bill Merriman, who received his brother's kidney in the first identical twin transplant performed in Virginia, leaving for his Oklahoma City home after the December 12, 1957 operation.

First cadaver kidney transplant at Medical College of Virginia, October 1962, survived 18 years.

Dr. Hume with Miss Dorsey.

Dr. Hume and Miss Dorsey with Dr. Williams.

By 1957, Dr. Hume had performed the first identical twin kidney transplant in Virginia on a patient named Bill Merriman from Oklahoma City. Dr. Hume reported later that this patient underwent a bilateral nephrectomy on an elective basis to control his intractable hypertension problem. He thought this probably was the first case of elective bilateral nephrectomy for this purpose. This experience was later reported by Dr. Ginn who accompanied the recipient from Oklahoma City and stayed with him in Richmond for a while. Since I was not a participant in this event, I don't know much about the details of this case (3).

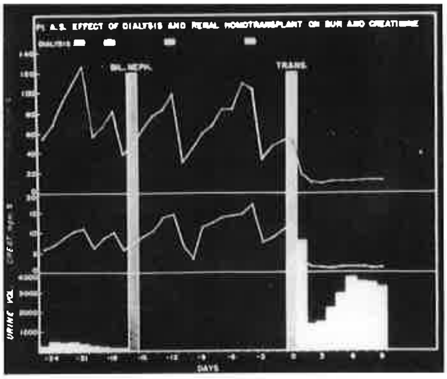
The surgical research laboratory was full of animal research activity, most of it relating to organ transplantation, but some were neuroendocrinology with surgical stress problems. We would be doing two to three paired kidney transplants in the mongrel dog, practically on a daily basis. One dog would be acting as a donor and recipient, swapping the kidney with the paired dog. We obtained the mongrels from the dog pound, carefully selecting the healthiest looking ones, and, following surgery, administered daily doses of intravenous 6-MP which came in powder form in the bottle. We nursed our dogs carefully with tender loving care to assure survival as long as possible since the death of the animal was the end point of the experiment. Many chemotherapy agents besides 6-MP were tried.

In 1961 I was back in clinical training, still partly involved in the research laboratory under the supervision of Dr. John Mannick who had arrived from Boston as a faculty member. In the summer of 1962 the clinical (homografts) kidney transplant program began at the University Hospital. The first four patients received total body irradiation as part of the immunosuppressive protocol. The first living-related donor recipient was a 15-year-old girl who received a kidney from her mother in 1962. I was involved in this case as a resident surgeon and recall how difficult it was to care for the patient postoperatively after she had received sublethal total body irradiation. This patient died four weeks following the transplant from complications of the sublethal total body irradiation with hemorrhage.

The second transplant was performed on October 24, 1962. This was a 26-year-old White male (blood type 0) from North Carolina. He had undergone elective bilateral nephrectomy to control his blood pressure 10 days prior to this date (4). The donor was a 52-year-old cadaver. Since the donor was cardiac dead with long ischemia time, the transplanted kidney did not function for over a month. Eventually this transplanted kidney maintained the patient without dialysis for over a year but slowly lost function and was finally removed February 11, 1964. This patient subsequently received a living-related donor kidney from his mother on April 8, 1964, survived for 18 years, dying with fulminant pneumonia January 30, 1983. This was one of the longest surviving total body irradiation kidney transplant patients in the world.

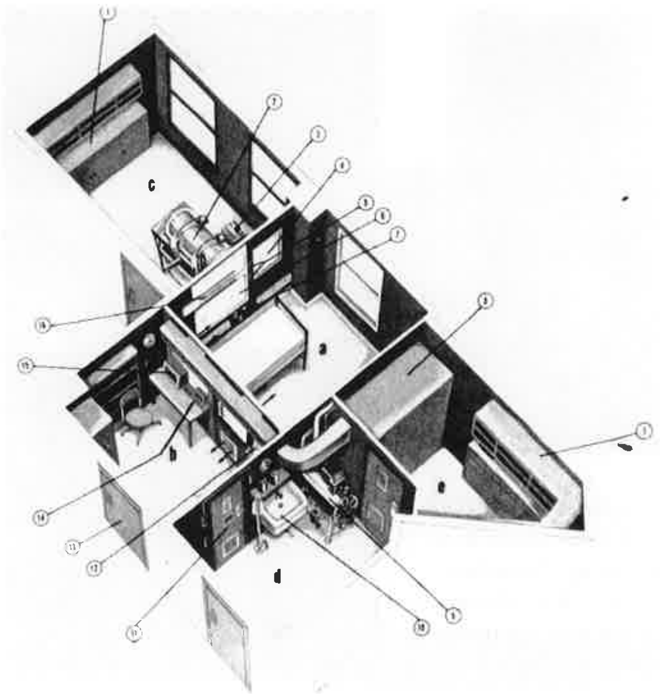
Two additional transplant patients also received sublethal total body irradiation: The next one was a 19-year-old young woman who received her sister's kidney which functioned nearly five years. This patient survived a total of eight years after having received four kidney transplants (the last three having been cadaver kidneys). The fifth patient to receive a kidney transplant was a 22-year-old White female who received her brother's kidney on March 18, 1963. This is our longest surviving kidney transplant patient, currently alive and well. The first successful second kidney transplant on the same patient was performed on a 37-year-old White male on August 3, 1963. This patient received his first kidney from his brother-in-law on April 17, 1963, which had to be removed on June 22, 1963 due to recurrent acute rejection.

Longest living-related donor (LRD) kidney transplant survivor (brother donor), March 1963.



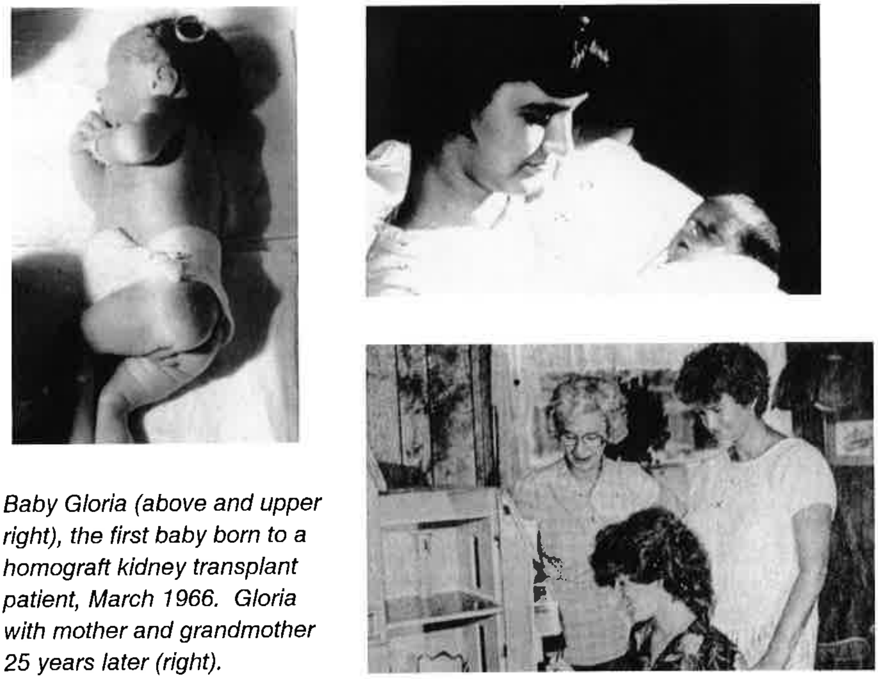
Longest LRD survivor, elective bilateral nephrectomy pretransplant.

Longest pediatric kidney transplant survivor, May 1963.



Pathogen-free patient care area (sterile room).Artist's drawing of area showing storage cabinets (1); "artificial kidney" in operating location (2); electrocardiograph machine (3); television viewing window (4); radio-TV and intercommunication system speakers (5); view window with one-way mirror (6); pass-ports for cannulas, tubes, etc. (7); air-conditioning unit with duct system (8); stream autoclave (9); scrub basin (10); entrance from scrubroom into anteroom (11); pass-port for materials (12); entrance door from ball into anteroom (13); recording thermometer (14); intercommunications master panel (15); portion of indirect ultraviolet light fixture (16); patient room (a); anteroom (b); "kidney" or work room (c); scrubroom (d); and utility room (e).

(Left to right) Drs. Lee, Bower, and Hume.



Baby Gloria (above and upper right), the first baby born to a homograft kidney transplant patient, March 1966. Gloria with mother and grandmother 25 years later (right).

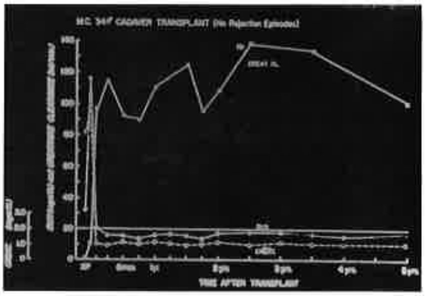
In spite of the then prevailing pessimism for the success of the second kidney transplant (no one having had a second kidney transplant survival experience), this patient received a second kidney transplant from a 32-year-old cadaver donor, survived, and returned to his original job of plumbing and died five years later with a cerebral vascular accident. This is believed to be the first successful second kidney transplant in the world.

The longest-surviving pediatric kidney transplant patient in our experience was performed on May 16, 1963.

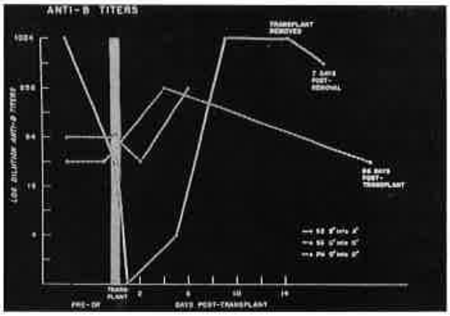
I should mention here that the earlier development of a sterile environment to care for total body irradiation patients was carefully designed by Dr. Max Rittenbury and constructed in one corner of the transplant unit (5). It was actually put into use and while it was effectively pathogen free for the purpose, I recall how cumbersome it was to go in to care for the patients. Total body irradiation as a method of immunosuppressive therapy was abandoned after treatment of four patients, but we continued to use the pathogen-free room whenever we had a patient who developed severe leukopenia. In 1964, an independent clinical transplant unit was opened with nine beds along with a 15-bed self care unit. Ms. Hinchy was the first chief nurse to preside over the early phase of the transplant unit transition. She remained with the transplant program for several years until she got married.

Nineteen hundred sixty-five turned out to be another eventful year. Dr. Mel Williams joined the faculty following training at Massachusetts General and experience at Eliza Hall in Australia. The tissue typing laboratory was opened that same year with the help of Drs. Amos and Terasaki. Dr. Richard Lower also joined as Chief of Cardiovascular Surgery with plans to start a cardiac transplant program.

But the most dramatic and memorable event was the birth of the baby Gloria. Twenty-one-year-old Kate G. (who received a kidney transplant from her mother on


CADAVER TRANSPLANT (No Rejection Episodes)
CREAT. CL.
TIME AFTER TRANSPLANT

The longest surviving cadaver kidney transplant recipient (above and upper right). Operation in April 1965.



Blood type AB mismatch (recipient=A$^+$, donor brother=B$^+$).

February 24, 1965) became pregnant almost immediately following her transplant; she had not had menses during the chronic renal failure period and was unaware of the significance of the lack of menstrual periods after the transplant. When she underwent an intravenous pyelogram on her follow-up visit, her pregnancy was discovered by the x-ray technician who took scout films and found the bony structure of the baby. She delivered a full-term baby on March 26, 1966 through vaginal delivery. This is believed to be the first baby born to a homograft patient through vaginal delivery. The baby grew up to be an intelligent, beautiful young woman, and all three - grandmother, mother, and daughter - are alive and well (6).

One of the longest surviving cadaver kidney transplants in the world, a 34-year-old white male who received a cadaver kidney on April 28, 1968, is currently 65 years old and surviving to this day in good health without having suffered any significant rejection episodes throughout the course. The second longest cadaver kidney transplant survivor in our experience was a 30-year-old black male who received a cadaver kidney on August 11, 1965 and is surviving well to this date (7).

At this point I should mention some other current research activities, most notably the development of antilymphocyte serum, rabbit antirat, in prolonging skin graft survival. This was done from 1960 to 1964 by Jerry Sacks, then a research fellow and junior resident from Minnesota (8). Subsequently, Kauffman and Dalton were involved in the development of horse antiserum to be used in the dog kidney transplant experiments. Mr. Millington, the technician who had been working with this project since Dr. Sack's early experiments, continued to be engaged in the development of rabbit antithymocyte globulin in our institution until his retirement only two years ago. In 1963, Cleveland and I developed a simple cold perfusion to preserve the kidney which was to be a standard protocol for us for a long time (9). Local irradiation was used to prolong the kidney transplant survival in the animal and later in the human. The report of this was the first paper that I ever presented at a medical meeting. I still recall how anxious and excited I was before the presentation and how depressed I was afterwards (10).

In 1966 we observed the first hyperacute rejection event in an ABO-mismatched kidney transplant as well as a primary graft in a multiple pregnancy woman. We began to realize that transplant rejection is not only mediated by cell-to-cell interaction but also by the humoral antibody. These experiences, coupled with one more experience with a second kidney transplant, were reported in detail by Mel Williams (11). In Dr. Lower's laboratory (12), the experiment for the preservation of the cadaver heart was going on in earnest with practical application in human cardiac transplantation. In one notable experiment, the cadaver heart was removed, taken to the laboratory, and hooked onto the cardiac perfusion machine, with the oxygenator. I vividly recall the excitement of Lower and Cleveland (then a research fellow) with this experiment. They made a movie of the procedure and presented it at some of the medical meetings, receiving varying responses, "some incredulous and some angry."

This was also the year that Dr. Christiaan Barnard visited from South Africa, ostensibly to learn organ transplantation before setting up his own program. He arrived in August and left at the end of October. In a letter written to Dr. Hume shortly after his return to South Africa, Dr. Barnard noted that the progress in his institution had been slow and somewhat discouraging, reminding Dr. Hume of his earlier offer to take him back. As we all know, he was to do a cardiac transplant in December 1967, the first in the world.

Collaboration with Dr. Terasaki's laboratory with regard to the correlation of the clinical course and rejection of the kidney transplant with histocompatibility matching was carried out in earnest. Some of these results were presented at the Santa Barbara Conference on Transplantation, chaired by Dr. Longmire in January 1967 (13).

When Dr. Peter Morris was visiting in Boston in 1967, he stopped by on the way home and contributed significantly to our tissue typing laboratory activity. My friendship with Professor Morris dates back to this period (14).

The most memorable event in my professional career occurred in 1967: attending the First International Congress of the Transplantation Society meeting in Paris. Not only was it the first European trip I had ever taken, but it was the first time I saw all the pioneers in the transplantation field: Sir Peter Medawar, Billingham, Professor Woodruff, Professor Hamburger, and others.

In our research laboratory, Drs. Braf and Rolley were beginning to develop antilymphocyte serum using the horse, goat, sheep, and rabbit and using them in animal studies as well as human trials in four patients.

HISTORY OF CLINICAL TRANSPLANTATION RESEARCH IN VIRGINIA

David M. Hume, M.D. Stuart McGuire Professor of Surgery
Chairman, Department of Surgery, Medical College of Virginia
Health Sciences Division, Virginia Commonwealth University

1956 - RESEARCH IN TRANSPLANTATION BEGAN

1957 - VIRGINIA'S FIRST IDENTICAL TWIN RENAL TRANSPLANT RECIPIENT

1962 - VIRGINIA'S FIRST HUMAN RENAL ALLOGRAFT PERFORMED

1964 - CLINICAL TRANSPLANT CENTER (9 Bed Capacity) AND SELF CARE UNIT (15 Bed Capacity) OPENED

1965 - TISSUE TYPING LABORATORY OPENS

1966 - VIRGINIA'S FIRST LIVER ALLOGRAFT PERFORMED

1966 - WORLD'S FIRST BABY BORN OF A MOTHER WITH A RENAL ALLOGRAFT

1968 - REGIONAL CADAVER ORGAN PROCUREMENT PROGRAM BEGAN

1968 - VIRGINIA'S FIRST CARDIAC ALLOGRAFT PERFORMED

SOUTHEASTERN CADAVER ORGAN PROCUREMENT PROGRAM

With tissue typing labs ●
Without tissue typing labs ○

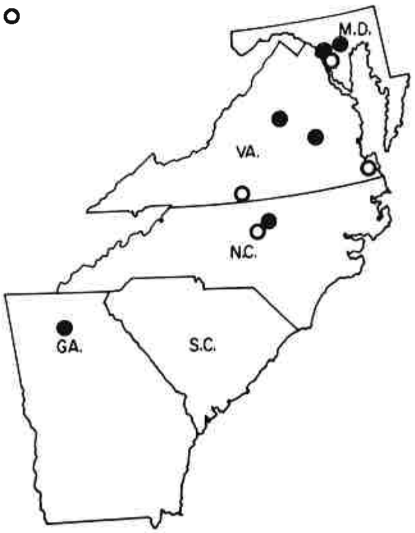
VIRGINIA
Medical College of Virginia - Richmond
University of Virginia - Charlottesville
Norfolk General Hospital - Norfolk
Danville Memorial Hospital - Danville

NORTH CAROLINA
Duke University - Durham
University of North Carolina - Chapel Hill

MARYLAND
John Hopkins University - Baltimore
University of Maryland - Baltimore

GEORGIA
Emory University - Atlanta

DIST. OF COLUMBIA
Georgetown University - Georgetown



On May 25, 1968, the first cardiac transplant was performed in Richmond. Eventually, this was to develop into the now famous "Tucker Trial" which defined "legal" brain death. The court session was held May 1972 in the State Law and Equity Court, presided over by Judge A. Christian Compton who later became a Supreme Court Judge of the Commonwealth of Virginia. The plaintiff's lawyer was State Senator L. Douglas Wilder, now the first elected Black Governor of the Commonwealth of Virginia. This eventually went to the Federal Court but was dismissed in

January 1973. Professor Fletcher, a medical ethicist, and Dr. Becker, a neurosurgeon, were among the expert witnesses, defining the concept of brain death as the "modern" definition of death.

During this period, interest in liver transplantation to treat end-stage hepatic failure patients was also in full swing. As a part of hepatic support, baboon cross perfusion experiments along with hypothermic human blood replacement of baboon blood for associated purposes were attempted in the laboratory. Many people were involved; Drs. Gayle and Klebanof (15) and later, Dr. Abouna, to mention but a few (16). The first liver transplant was attempted in 1968. One of the liver transplant patients survived over a year and died with recurrent hepatoma.

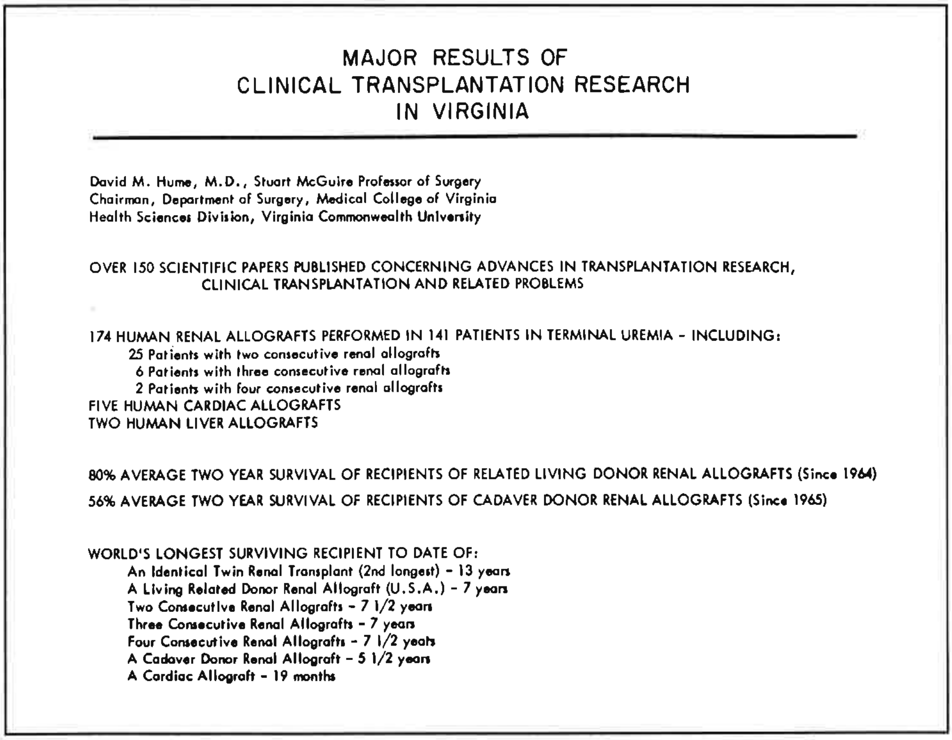
Along with the development of histocompatibility testing approaching the clinical application, the concept of organ exchange to test the utility of histocompatibility matching was developed by Professor Amos at Duke and Dr. Hume. With four institutions as a core, (Duke, Johns Hopkins, the University of Virginia and the Medical College of Virginia), the first meeting of the Southeastern Regional Organ Procurement Program was developed. The Belzer perfusion machine was purchased, placed in the van with a hydraulic lift to transport the kidney in cold perfusion. For longer distances, the State Police or the Air Force was mobilized. Since the State Police could not cross the state border, this had to be coordinated from the State Police to State Police (in bordering states). I still recall with amazement both their cooperation and well-coordinated transportation. Eventually in 1968 this program was expanded to include nine institutions funded by the Public Health Service; Southeastern Organ Procurement Foundation (SEOPF), based in Richmond and Duke, was the beginning of the organ exchange network based on histocompatibility matching in North America.

In May 1977, the first long distance cadaver heart procurement was performed under the umbrella of SEOPF and the United Network for Organ Sharing (UNOS), transporting the heart from Indianapolis to Richmond with success.

By the early 1970s, Dr. Hume had a very strong interest in producing antithymocyte serum to be used in human clinical transplantation. Dr. Shanfield, from Montreal, joined us helping in this area since he had published a paper with regard to the production of the effective antihuman thymocyte globulin. He was involved in the production of the human antithymocyte serum produced in the horse, assayed in the monkey skin graft. During this period, five clinical transplant patients received this antithymocyte serum on an experimental protocol. To increase efforts in this area, Dr. Hume recruited Judy Thomas who was engaged in earnest production of the antithymocyte globulin, standardization, and bioassay of the immunosuppressive effect.

With an increasing number of kidney transplants being performed all over the world in the clinical setting, Dr. Hume organized the First International Symposium on Clinical Organ Transplantation, sponsored by the International Transplantation Society, in Richmond, May 22 to 24, 1972. The participants included the "Who's Who" of the transplantation field from all over the world. The program included immunological background, and kidney, liver, and heart transplantation.

My recollection of the early days of organ transplantation in Richmond ends with Dr. David M. Hume's untimely death in a plane accident in May 19, 1973. He was a pioneer in organ transplantation in modern medicine, a restless genius, and a compassionate clinician who was also my mentor and friend. He passed away leaving a legacy of advancement in modern medicine which brought relief in human suffering.



MAJOR RESULTS OF CLINICAL TRANSPLANTATION RESEARCH IN VIRGINIA

David M. Hume, M.D., Stuart McGuire Professor of Surgery
Chairman, Department of Surgery, Medical College of Virginia
Health Sciences Division, Virginia Commonwealth University

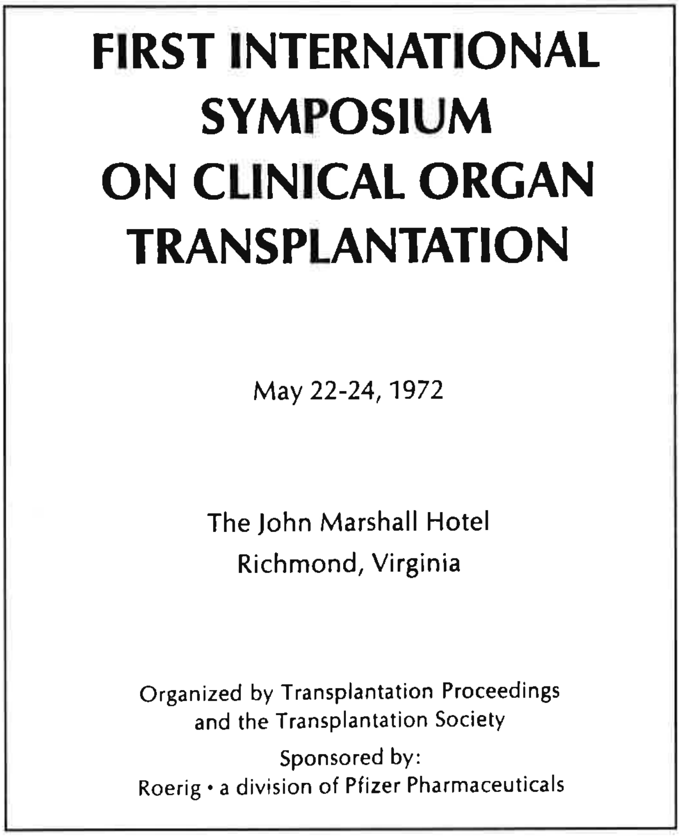
OVER 150 SCIENTIFIC PAPERS PUBLISHED CONCERNING ADVANCES IN TRANSPLANTATION RESEARCH, CLINICAL TRANSPLANTATION AND RELATED PROBLEMS

174 HUMAN RENAL ALLOGRAFTS PERFORMED IN 141 PATIENTS IN TERMINAL UREMIA - INCLUDING:
  25 Patients with two consecutive renal allografts
  6 Patients with three consecutive renal allografts
  2 Patients with four consecutive renal allografts
FIVE HUMAN CARDIAC ALLOGRAFTS
TWO HUMAN LIVER ALLOGRAFTS

80% AVERAGE TWO YEAR SURVIVAL OF RECIPIENTS OF RELATED LIVING DONOR RENAL ALLOGRAFTS (Since 1964)

56% AVERAGE TWO YEAR SURVIVAL OF RECIPIENTS OF CADAVER DONOR RENAL ALLOGRAFTS (Since 1965)

WORLD'S LONGEST SURVIVING RECIPIENT TO DATE OF:
  An Identical Twin Renal Transplant (2nd longest) - 13 years
  A Living Related Donor Renal Allograft (U.S.A.) - 7 years
  Two Consecutive Renal Allografts - 7 1/2 years
  Three Consecutive Renal Allografts - 7 years
  Four Consecutive Renal Allografts - 7 1/2 years
  A Cadaver Donor Renal Allograft - 5 1/2 years
  A Cardiac Allograft - 19 months



FIRST INTERNATIONAL SYMPOSIUM ON CLINICAL ORGAN TRANSPLANTATION

May 22-24, 1972

The John Marshall Hotel
Richmond, Virginia

Organized by Transplantation Proceedings
and the Transplantation Society

Sponsored by:
Roerig • a division of Pfizer Pharmaceuticals

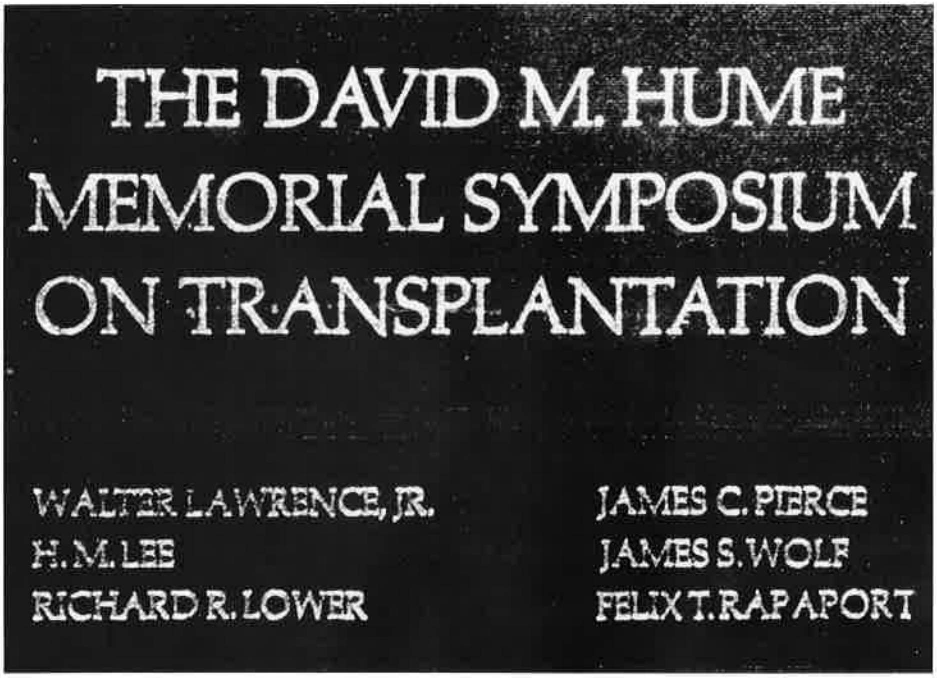
DAVID M. HUME, M.D.
Stuart McGuire Professor and Chairman
of the Department of Surgery,
Medical College of Virginia.
1956-1973

Dr. David Hume.

Dr. Hume with LRD transplant recipient (still alive well over 20 years later) in 1972.

POSTSCRIPT

In memory of Dr. David M. Hume, the David M. Hume Memorial Symposium was organized and held in Richmond from April 24 to April 25, 1974. The comrades in arms of the transplant field from the world over gathered for this special occasion. In Dr. Francis Moore's eulogy at the memorial service, he said: "Genius perceives the way of the future through the orderliness of nature. It has been said that nature poses no problems, only solutions. Genius finds these solutions and puts them to work for mankind. A restless person is one who is dissatisfied with things as they are. His restless spirit leads him to adventures and new ideas, but also to controversy and sometimes to danger. He often upsets or disturbs those who would keep things as they are, or move more slowly. David Hume's *restless genius* did all these things." Were he here today, to listen as we celebrate his life and the affection that all of us feel for him, and as we mourn the loss of his early passing, he would modestly turn us aside with a joke. But in his heart he would rejoice that we were here and that we all understand why thousands of people today...all over the world...owe their lives to what his restless genius, dissatisfied with things as they were, lead him to do for the first time."



THE DAVID M. HUME
MEMORIAL SYMPOSIUM
ON TRANSPLANTATION

WALTER LAWRENCE, JR.
H. M. LEE
RICHARD R. LOWER

JAMES C. PIERCE
JAMES S. WOLF
FELIX T. RAPAPORT

The David Hume Memorial Symposium.

Dr. Ascher Sir Peter Medawar

Dr. Najarian Sir Peter Medawar

Dr. Najarian Dr. Penn

Dr. Cortesini

Professor Billingham

Dr. Takagi Dr. Sutherland

Professor Morris

Professor Morris Professor Sheil

Dr. Rapaport Professor Morris

Dr. Salvatierra Dr. Maki Dr. Terasaki

Dr. Butt Dr. Ochiai

Dr. Penn Dr. Wolf

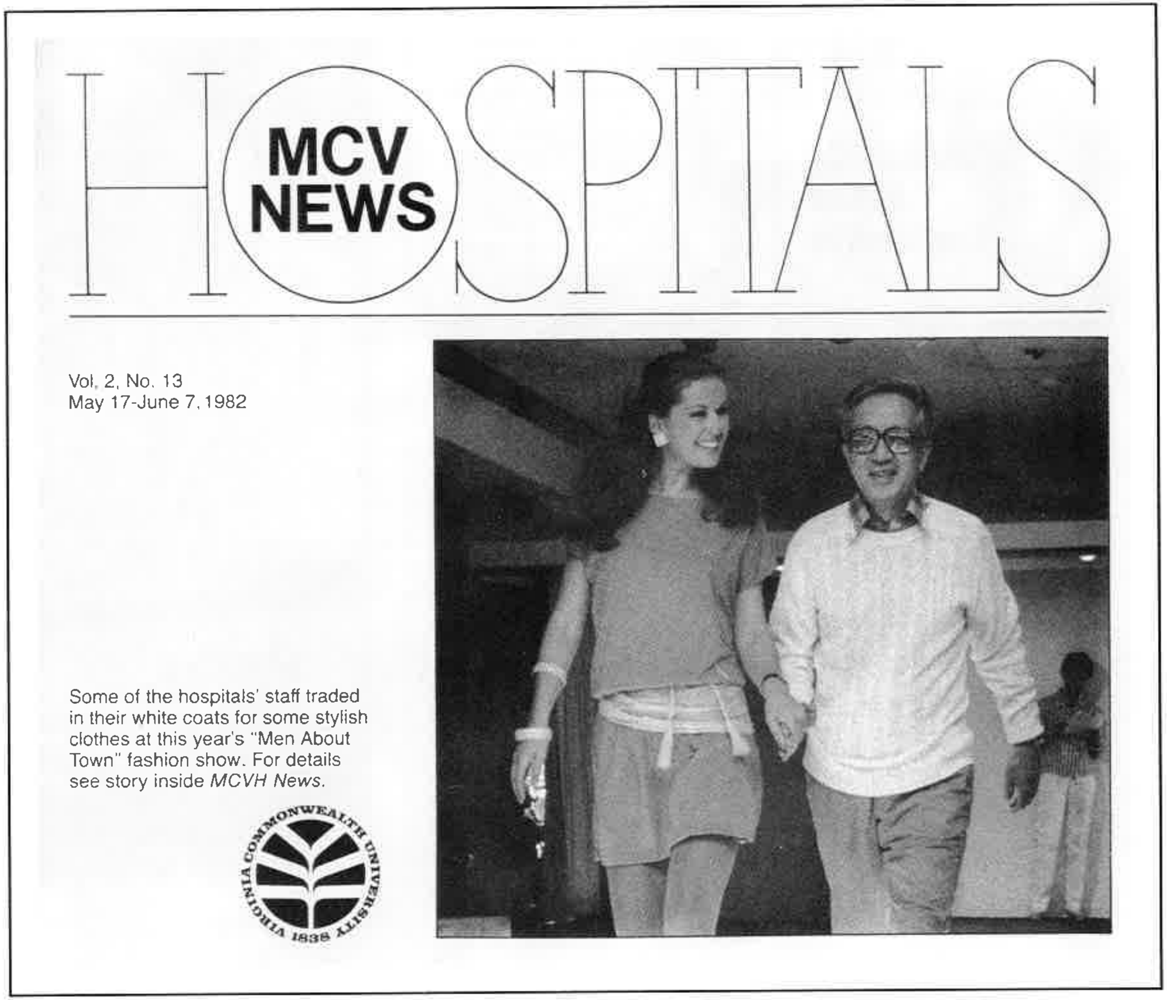
Dr. Slapak

Dr. Posner Dr. Hardy

Professor van Rood Dr. Van Hooff

Dr. Russell Professor Brent

Dr. Ohta from Japan



HOSPITALS MCV NEWS

Vol. 2, No. 13
May 17-June 7, 1982

Some of the hospitals' staff traded in their white coats for some stylish clothes at this year's "Men About Town" fashion show. For details see story inside *MCVH News*.

VIRGINIA COMMONWEALTH UNIVERSITY 1838

REFERENCES

1. Hume DM, Jackson BT, Zukoski CF, et al. The homotransplantation of kidneys and of fetal liver and spleen after total body irradiation. Trans 80th Am Surg Assoc 1960; 78:12. Ann Surg 1960; 152:354.
2. Zukoski CF, Lee HM, Hume DM. The prolongation of functional survival of canine renal homografts by 6-mercaptopurine. Surg For 1960; 11:470.
3. Ginn HE, Jr, Unger AM, Hume DM, et al. Human renal transplantation: An investigation of the functional status of the denervated kidney after successful homotransplantation in identical twins. J Lab Clin Med 1960; 56:1.
4. Prout GR, Jr, Hume DM, Magee JH, et al. Bilateral nephrectomy: Its role in renal homotransplantation and the anephric state in man. Trans Am Urol Assoc 1964; (abstract).
5. Rittenbury MS, Hume DM, Hench DM. Pathogen-free patient care area. In: Sylvester JC, Ed. Antimicrobial Agents and Chemotherapy - 1962. Proc Second Interscience Conference of Antimicrobial Agents and Chemotherapy, Chicago. American Society for Microbiology, Ann Arbor, 1963; 51.
6. Board JA, Lee HM, Draper DA, et al. Pregnancy following kidney homotransplantation from a non-twin. Report of a case with concurrent administration of azathioprine and prednisone. Obstet Gynecol 1967; 29:318.
7. Hume DM, Magee JH, Prout GR, Jr, et al. Studies of renal homotransplantation in man. Ann NY Acad Sci 1964; 120:578.
8. Sacks JH, Filippone DR, Hume DM. Studies of immune destruction of lymphoid tissue: I. Lymphocytoxic effect of rabbit-anti-rat lymphocyte antiserum. Transplantation 1964; 2:60.
9. Cleveland RJ, Lee HM, Prout GR, Hume D.M. Preservation of the cadaver kidney for renal homotransplantation in man. Surg Gynecol Obstet 1964; 119:991.
10. Lee HM, Kauffman HM, Cleveland RJ, et al. Selective immunosuppression by local radiation of renal homografts. Surg For 1964; 15:158.
11. Williams GM, Lee HM, Weymouth RF, et al. Studies in hyperacute and chronic renal homograft rejection in man. Surgery 1967; 62:204.
12. Williams GM, Hume DM, Hudson RP, Jr, et al. "Hyperacute" renal-homograft rejection in man. N Engl J Med 1968; 279:611.
13. Lee HM, Hume DM, Vredevoe DL, et al. Serotyping for homotransplantation. IX. Evaluation of leucocyte antigen matching with the clinical course and rejection types. Transplantation 1967; 5:1040.
14. Morris PJ, Hume DM, Terasaki PI. The development of cytotoxic antibodies in renal transplantation. In: Curtoni ES, Mattiuz P, Tosi RM. Histocompatibility Testing 1967. Williams and Wilkins, Baltimore, 1967; 229.
15. Hume DM, Gayle WE, Jr, Williams GM. Cross circulation of patients in hepatic coma with baboon partners having human blood. Surg Gynecol Obstet 1969; 128:495.
16. Hume DM, Mendez-Picon G, Gayle WE, Jr, et al. Current methods of support of patients in hepatic failure. Transplant Proc 1971; 3:1525.

CURRICULUM VITAE

Hyung Mo Lee

PERSONAL

Born: October 17, 1926
Citizenship: United States
Marital Status: Married; 2 children
Home Address: 8705 Standish Lane
Richmond, VA 23229
Office Address: Medical College of Virginia
Department of Surgery
1200 E. Broad Street
Richmond, VA 23298

EDUCATION

1945	Keijo Imperial University, B.S.
1949	Seoul National University Medical School, M.D.

LICENSURE

1965	American Board of Surgery
1983	Vascular Surgery Board

POSITIONS

1953-54	Intern, James Walker Memorial Hospital, Wilmington, North Carolina
1954-55	Intern, Stuart Circle Hospital, Richmond, Virginia
1959-61	Surgical Research Fellow, Medical College of Virginia
1955-57/1961-62	Assistant Residency, Medical College of Virginia
1962-63	Residency, Medical College of Virginia
1963-64	Instructor of Surgery, Medical College of Virginia
1964-66	Assistant Professor of Surgery, Medical College of Virginia
1966-70	Associate Professor of Surgery, Medical College of Virginia
1970-	Professor of Surgery, Medical College of Virginia
1973-	Director, Clinical Transplant Program, Chairman, Division of Vascular and Transplant Surgery, Medical College of Virginia, Director, Clinical Transplant Fellowship Program
1986-	Director, Vascular Fellowship Program

PROFESSIONAL SOCIETIES

American Association of University Professors
American College of Surgeons
American Society of Nephrology

	American Society of Transplant Surgeons 1981-83 Secretary 1984-85 President
1985-	Board of Directors, Chairman Asian American Health Forum
	Humera Society
	International Cardiovascular Surgical Society
	International Society for Heart Transplantation
	International Society of Nephrology
1984-85	President, Korean Medical Association of America
	Medical Society of Virginia
1984-	Medical Advisory Board , National Kidney Foundation of Virginia
	Network Coordinating Council of the Virginias 1983-84 Executive Board 1984-85 Medical Review Board
	New York Academy of Science
	Renal Physicians Association
	Richmond Academy of Medicine
	Richmond Surgical and Gynecological Society
1988-89	Board of Directors, Seoul National University College of Medicine Alumni Association
	Society for Clinical Trials
1979-80	President, Southeastern Organ Procurement Foundation
	Southeastern Surgical Society
	Southern Association for Vascular Surgery
	Transplantation Society
	Virginia Surgical Society
	Virginia Vascular Society

AWARDS

1978	Alpha Omega Alpha Honorary Society
1990	University Award of Excellence, Virginia Commonwealth University
1990	MCV Alumni Association, Distinguished Faculty Award

COUNCIL AND ADVISORY COMMITTEE MEMBERSHIPS

1984	Grievance Committee
1984	Product Evaluation Committee
1984	Medical Care Evaluation (University)
1984-88	Ethics Committee (University)
1985-87	Advisory Committee for Richmond Metropolitan Blood Service (State)
1987-89	Tenure and Promotions Committee for MCV School of Medicine (University)
1987-	Graduate Medical Education Committee (University)
1990-	Foreign Relations Committee UNOS (International)
1991	Credentials Committee (University)

TRANSPLANTATION: A CANADIAN CAREER-GIVING EXPERIENCE

John B. Dossetor

Address: Bioethics Project
222 ANR
8220 114th Street
Edmonton, Alberta, Canada

John B. Dossetor

1960

1990

TRANSPLANTATION: A CANADIAN CAREER-GIVING EXPERIENCE

John B. Dossetor

Initiation Rites

It all started by a coincidence: the admission to the Montreal Neurological Institute of an adolescent girl of 15 with convulsions. It was a Monday in late March 1958, and I was the renal physician on call. She was severely hypertensive and in uremia. Subsequently, an open renal biopsy confirmed a diagnosis of chronic pyelonephritis.

As a junior consulting physician, I was one of two nephrologists in a recently formed renal service. Robert O. Morgen (later at Baylor, and then Aspen, Colorado) was the other. We were proud of the emergence of this new service, inspired by a questionable capacity for treating acute renal failure by hemodialysis, a conceit in manipulating electrolyte imbalance, and proven dexterity in wielding the renal biopsy needle. There was no formal training for nephrology in those days. In internal medicine circles, nephrology was the "new kid on the block."

As colleagues, we had agreed that each would "stay with" patients on whom we had been consulted even when doing relief coverage during the other's on-call month. I had been covering for him that weekend as he, Bob, was enjoying some early spring skiing in the Laurentians. Indeed, I agreed to extend this cover for an extra day, the day on which this young patient had been admitted. Little did I realize that this particular consultation would change my whole professional career; indeed, it changed my life.

The patient turned out to have an identical sister. This fact was discovered by the resident, Helene Desjardins, and it was she who suggested that an identical-twin transplant might be a possibility. The first identical-twin experience from Boston came in 1956 (1), followed by an article on eight identical-twin cases (2) with impressive results. We considered sending our patient to Boston, but the twins were part of a closely knit family of five daughters and one son; their mother, strongly supported by the rest of the family, resolved to have her daughter stay at the Royal Victoria Hospital in Montreal and "take her chances" there.

Before the transplantation event (eventually done on May 25, 1958), a family court judge had to grant the parents the right to give permission for nephrectomy ("a mutilation procedure") on the healthy twin, and skin grafts were exchanged to demonstrate lack of rejectivity. Another small incident sticks in one's mind: Having said at a press conference that I supposed even their fingerprints were identical, I was surprised to receive a call a few days later from the Royal Canadian Mounted Police who told me they understood that the only features that were never identical in identical twins were their fingerprints. They were quite right, of course!

Preparations for this first transplantation were prodigious even though there was no need for clinical immunosuppression (a term whose time was yet to come). It was decided not to carry out hemodialysis (this was in the early days of widespread availability of that mode of treatment in Montreal) as our experiences in acute renal failure–largely because it was undertaken too late–had been discouraging. She was submitted to transplant surgery as soon as possible. The surgical team was comprised of Joe C. Luke (vascular) and Ken MacKinnon (urology), and I was the renal physician (supported by John C. Beck and Bob Morgen). A special resident was assigned to look after just this case; he carried out three hourly fluid and electrolyte balances several times daily on an enormous wall chart, using a slide rule. The initial diuresis was 800 ml in the first hour. Three nurses were assigned for the duration of this case. It was clearly excessive but reflects the uncertainty of the management team.

The surgery was relatively uneventful, though the donor ureter was deemed inadequate so the recipient ureter was used with pelvi-ureteric anastomosis. These moments one does not forget, though my participation as nephrologist in the OR was that of a "loose cannon on the deck!" In retrospect, the postoperative course was smooth, but the electrolyte, fluid, and nitrogen balance data, together with observations on mechanisms of renal hypertension, disappearance of secondary hyperparathyroidism, reestablishment of protein anabolism, the nature of diurnal excretory rhythms after renal denervation, and other features, were copious enough to result in two publications (3,4). It was also a dramatic illustration of what transplantation might do to uremia in the absence of the rejection process.

The Dawn of Clinical Renal Allografts

It was as recently as 1955 when the principal question regarding homograft failure was "Is the homograft rejection an immunological response?" (5). At the New York Academy's second tissue homotransplantation conference, the immunologic significance of rejection of skin grafts was accepted, and it was envisioned that use of skin homografts in plastic surgery would ultimately "exceed wildest imagination" (6). Organ transplantation, not skin, was first mentioned at the meeting of the New York Academy of Science in 1960, where dismal results were reported for high-dose irradiation alone (7), though by the 1962 meeting, Hamburger was able to report some success from irradiation when living-related donors were used (8).

In 1963, the McGill group, with Lloyd MacLean as Chief of Surgery, decided to undertake a limited experience in allogeneic (the word was just becoming popular, replacing "homologous") renal transplants obtained from cadaveric sources. This was made feasible by the demonstration of how to use azathioprine (BW 57-322), steroids, actinomycin D, and local x-irradiation from Murray and Calne's epoch-making work initially on dogs (9) and then in patients (10). However, early results were not encouraging. At a Washington meeting in September 1963, the then world experience showed that only 23 of 96 grafts functioned at six months, and only seven of 23 at one year (11). The McGill's initial report on four cadaveric allografts could claim only one long-term survivor (12). How would these results have fared on ethics review, one wonders?

One is aghast to recall the precautions taken to avoid extraneous infection in the first few cases on azathioprine. A special suite was constructed with elaborate entrance chambers and scrub sinks. I recall that prepared food, reading and writing materials, and even the patient's cigarettes were gas sterilized. It took about 10 minutes to get into the inner sanctum. Not surprisingly, patients reacted psychologically to being treated like holy relics, expressing a strong aversion to such isolation. Furthermore, a tendency developed in staff to inquire about progress, not examine the patient for oneself. It did not take long to realize that the organisms to fear were the patient's own flora and that these precautions were relatively useless.

Immunology was a closed book to most internists in those days, even those who tried to struggle with the Prausnitz-Kustner passive-transfer skin test, passive cutaneous anaphylaxis, and other ways of demonstrating antigen-antibody reactions. It was the frustrated allergists who insisted that clinical transplant immunology was a new discipline in clinical immunology, and that transplant immunosurgeons and immunophysicians (largely nephrologists) had better "get with it," themselves. Clinical heartbreaks were frequent in those early days: transfer of carcinoma as an infiltrate in donor kidney; transfer of histoplasmosis; the miseries of ureteric fistulae; the pathos from excessive use of steroids. Yet there were also moments of high satisfaction in seeing uremia rapidly disperse and wellbeing strikingly restored. One simply overlooked the fact that there was little understanding of associated immune events - a fact recognized, but not condemned, by Sir Peter Medawar when he acknowledged around 1974 that if clinical teams had waited for the word "Go!" from basic immunologists, no human allografts would yet have been performed.

Before "Nonfunction on the Table" Was Perceived To Be Immunologic

Immediate nonfunction, with the kidney going a soft blotchy purple within minutes - now recognized as hyperacute rejection - was a baffling enigma. As yet, the immunological basis of this was not suspected, itself a surprising fact since accelerated rejection of second-set skin grafts in rodents was well described. Looking back at the early days of renal allografting, one can now realize that *immediate nonfunction was distinctly uncommon*. When it first occurred in the Montreal series, the crude notion was even entertained that the vessels had been inadvertently wrongly anastomosed - a suggestion not accepted with grace by my surgical colleagues! The lymphocytotoxic crossmatch was not yet in the literature, and no immunologic testing preceded transplantation.

Working with Jung Oh in Montreal, we stumbled across the toxicity of some serums to lymphocytes whilst trying to develop a bioassay for azathioprine using lymphocyte uptake of a radiolabelled thymidine as cell viability marker (13). Certain sera were very inhibitory, but this could not be due to azathioprine since toxicity remained even after transplant nephrectomy and cessation of immunosuppression. Of course, this inhibitory effect was due to lymphocyte antibody. Almost simultaneously, Kissmeyer-Nielson (14) showed that immediate renal nonfunction was immunologic, and the lymphocytotoxic pretransplant crossmatch rapidly became mandatory to prevent hyperacute rejection.

Denver's "Rocky Mountain High"

Tom Starzl in Denver, Colorado, hit the transplant scene in a big way in 1965. He had been in the early work in renal transplantation, but between November 1962 and March 1964, his team performed 64 living-donor renal transplants (46 living-related, 18 living-unrelated), when others were doing renal transplants at a deliberate but slow rate. The report in 1965 took the medical world by storm (15), with a further report nine months later (16). Many of us thought he was "putting himself out on a limb" by doing so many, so quickly, before the long-term results of the early ones were known. We were wrong. He took the subject from "clinical research" to "established procedure" in a few short months. World opinion soon changed from skepticism (tinged with awe) to frank admiration. Now we can add a fourth sentiment: gratitude. It is mentioned here as it had an effect in consolidating clinical renal allograft programs in other centers, too.

Pretransplant Blood Transfusion: Effect on Graft Function

These successes lulled one into thinking the human model must be immunologically different from animal models. In those days, dialysis patients were exposed to four units of allogeneic WBC-containing RBC each week as Kolff dialysis coils needed priming with two units of blood at each dialysis. Some of us vaguely wondered why all this blood did not cause more trouble.

HLA presensitization should have been extremely common in those dialysis patients, but it cannot have been. Indeed, on further analysis, the remarkable fact emerged that *greater allogeneic exposure*, at least in the uremic subject using the intravenous route, was associated with *better graft survival and reduced clinical rejectivity*! These observations led to a belief, and then a policy, that it was better to have dialysis for at least six months, or receive at least 100 units of blood from other people, to optimize cadaveric allograft survival! This very unusual fact was reported at a meeting in Santa Barbara at the end of 1966 (17).

It is still not fully explained why massive blood transfusion did not give rise to widely reactive lymphocytotoxic antibodies, as other allogeneic exposure does, though of course theories abound to explain the phenomenon. The "blood-transfusion effect" was subsequently repeatedly claimed, up to the end of the azathioprine era (1978-1979). In passing, one should emphasize that what is called "multiple blood transfusions" in the 1980s (say, 10 units of blood) would have been looked upon as mild allogeneic exposure by blood in the late 1960s.

Human Cross-Circulation to Establish Mutual Tolerance

The conviction that allogeneic exposure did immunologic good for subsequent organ transplants led to a unique experience in cross-circulation between two patients (18). At that time there were no Canadian transplant programs further east than Montreal. It was not unusual for patients to be referred for renal failure management from as far east as Newfoundland. However, management of such patients after transplantation was deemed to be impossible if they were not readily available for intensive follow-up. So, when a physician called about a uremic woman in Burgeo, on the south coast of Newfoundland (then accessible at certain times only by sea), he was told that nothing could be offered. He sent the patient just the same.

She was in her mid-30s and the mother of five. It was soon confirmed that little could be offered for management of her uremia, so it was agreed that we would dialyze her several times and then arrange transfer back to the Rock. However, a medical resident noticed that she had the same major blood group as another young woman who was dying of alcoholic cirrhosis. We speculated that, if exposure to blood were good, maximum benefit would be obtained by pretransplant cross-circulation. This idea germinated into the following plan: Both patients would be offered intermittent cross-circulation, with anticipated improvement in both of their vital end-organ failures. They would live symbiotically for as long as possible. In the event that one died, the vital organ which the other needed would be transplanted, be it liver or kidney, in the hope that by then some form of immunological tolerance would have been established. After a family conference, consent was signed for the procedure. There were no ethics committees in existence at that time, so there was no need for further clearance.

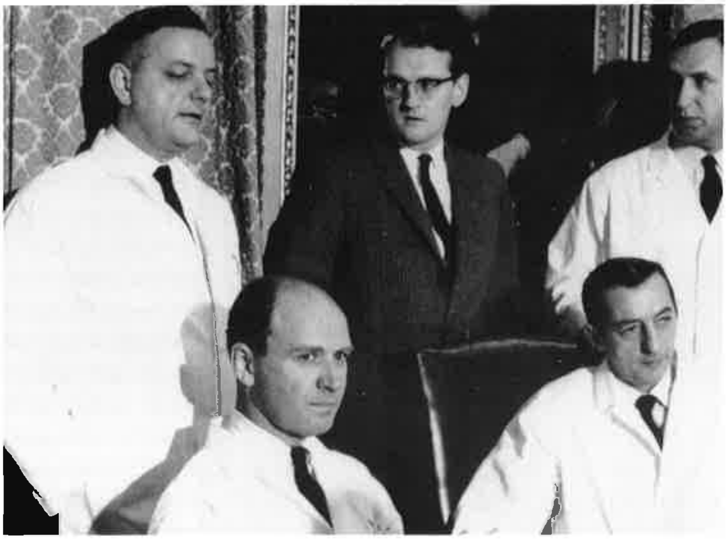
Cross-circulation had been used in unusual circumstances by others, such as Lillehei, for life-saving congenital heart surgery using parents for donor circulation, prior to introduction of the bypass membrane oxygenator (19).

Straight silastic catheters for interpatient arteriovenous cross-circulation were set up using a finely adjustable screw clamp on one of the lines for control of intercorporeal blood exchange. The extent of the latter was measured by having each patient lie on a sensitive bed scale, the weight of each could be reciprocally adjusted by fine tuning this single-line clamp.

There were two 36- and 24-hour periods of cross-circulation in the first week. During each of these periods, hepatic precoma in one and uremic precoma in the other improved dramatically. All blood

1963 (Clockwise from upper left)
J.B. Dossetor,
F.G. Inglis,
E.D. Monaghan,

K.J. MacKinnon,
L.D. MacLean



VII International Histocompatibility Workshop, Oxford, 1977

Canadian contingent (left to right)
M. Schroeder, A. Sargent, F. Pazderka, J. Wade, J. Dossetor, N.R. Sinclair,
H. Mervart, C.E. Reeve

John and Margaret Dossetor

(Left to right) Jean Dausset, John Dossetor, Joy Schlaut, and T. Kovithavongs

John Dossetor

parameters became identical in each patient during cross-circulation except for a somewhat higher BUN and creatinine in one, and a higher bilirubin in the other. On the 10th day, when cross-circulation was not in progress, but a third episode was being planned, the cirrhotic patient had a massive gastrointestinal hemorrhage which caused her demise. It took many hours to arrange for the cadaveric transplantation (it being Labor Day holiday) so there was a long period of posttransplant nonfunction of the renal allograft. During this time, the renal transplant team (and your scribe in particular) walked the hospital corridors in a cloud of unethical suspicion. However, diuresis occurred on the 19th postoperative day, and within a week there was normal renal function. She enjoyed nine years of excellent renal function back in Newfoundland, having a subsequent sixth pregnancy. Follow-up was limited to yearly or so visits to Montreal. It is difficult not to believe that cross-circulation rendered her tolerant in some way to the antigenic constituents of her cross-circulation partner's kidney, though this cannot be proved, of course. Seldom would circumstances arise that would justify not using more conventional management, though it is ironic to recall, however, that similar circumstances did recur a few years later. On this second occasion, the proposal for cross-circulation was turned down by the newly instituted ethics committee.

The Era of the "Plateau" in Renal Allograft Results

By 1970 there were several changes, now well established in dialysis programs, which had impact on renal transplant results (though they were not realized at the time). Dialysis was carried out three times weekly instead of twice. Dialyzers were much more efficient and did not require priming with allogeneic blood. This better control of uremia, which led to the virtual disappearance of uremic peripheral neuritis, was associated with great reduction in high blood transfusion requirements, with its associated hypersplenism. Thereafter, as mentioned already, the term "multi-transfused" carried the inference of 10 or more units, not 100 or more.

However, cadaveric transplant results did not improve. Indeed, the period of 1972 to 1977 was referred to as a period of "plateau of achievement" despite increasing proficiency of transplant teams. In retrospect, it seems reasonable to speculate that this plateau reflected improved management and technical efficiency balanced by less pretransplant blood-induced immunologic facilitation or "tolerance." The era of massive exposure to blood products had passed. The one-year renal allograft survival was about 70 percent with a five-year figure of about 50 percent.

All this was blown away, of course, by the cyclosporine era, which arrived towards the end of the 1970s and has dominated since.

Field Trip Adventures in Tissue Typing

The decade of the 1970s was of great significance to the growth of clinical histocompatibility with astonishing expansion of knowledge of the main histocompatibility complex (MHC). HLA international workshops were held every two years at such places as Los Angeles (the fourth, Terasaki, 1970), Evian (the fifth, Dausset, 1972), Aarhus, Denmark (the sixth, Kissmeyer-Nielsen, 1975), Oxford (the seventh, W. and J. Bodmer, 1977), Los Angeles (the eighth, Terasaki, 1980) - and they have continued through the 1980s. There was also a notable meeting on the association of HLA factors and disease (Paris, Dausset and Svejgaard, 1977). As part of these international efforts, there were interesting roles for "minor" players in this league. For this writer, this was especially true during the years when there was a search for those lymphocytes which could only stimulate with one haplotype in the mixed leukocyte culture (MLC) - because the x-irradiated cells were homozygous for HLA-A,B,(C), and DR. In fact, the unique property of these cells was homozygosity for a single DR antigen. They were termed "homozygous MLC typing cells," and a panel of them served to identify the DR antigen system of HLA.

The adventure of finding homozygous typing cells lay in their frequency in isolated human populations. For us in Edmonton, this meant taking advantage of our contacts with two such populations: the Inuit (Eskimos) of the Northwest Territories of Canada, and the Hutterite colonies in Alberta. In the early 1970s we made several expeditions to Iglooik (an island in Northern Hudson's Bay) and to Inuvik, Aklavik, and Tuktoyuktuk (at the Mackenzie river delta). The coldest experience of my life was unloading a propeller driven plane at -50°C, at night in Iglooik, in the slipstream created by the aircraft's propellers. The chill factor was phenomenal. The pilot would not permit his motor to be turned off for fear he could not get it going again! The yield of homozygous cells made it worthwhile, as well as the whole experience of life above the Arctic Circle. The parents of one notable family were homozygous for the same haplotype, all the siblings tested identically serologically, and there was no MLC stimulation in any combination between family members!

As for the Alberta Hutterites, we were welcomed into about 25 of the Dariusleut Colonies within a 150 mile radius of Edmonton, each with about 100 inhabitants. Sibships were commonly above 10 in number, and HLA haplotypes showed great restriction. The Dariusleut were all descended from the few founding families who came over from Russia in the mid-19th century (their final resting place after three centuries of European persecution). Newcomers very seldom enter the gene pool (despite rumors to the contrary). Their lymphocytes were harvested in exchange for a survey for hyperglycemia and hypertension, and those who had good "typing cells" were subsequently very generous with their blood.

Their generosity was not needed for long, as within a year or two, it was realized that platelet-absorbed sera could be used to detect DR antigens by simpler serological methods on preparations of pure B lymphocytes.

The Value of Reminiscence?

Despite its fascination, is there value in reminiscences of this sort? The prime mover of this book, Paul Terasaki, thinks there may be; so, hopefully, will the reader. The problem is that so much is left out, and what is included is slanted by personal bias and preference. This account, for instance, does insufficient credit to the whole MHC story though, fortunately, this has been very ably put together by a recent publication (20). Nor is there mention of the remarkable events which led to acceptance of criteria for determination of death from cerebral causes - brain death. This has made a major contribution to the subject of organ transplantation. This account is but the reminiscence of one Canadian physician who had the great good fortune to become involved in clinical renal transplantation in 1958 and whose career has been dominated by that circumstance ever since. It has proved to be a career-giving experience, indeed.

REFERENCES

1. Merrill JP, Murray JE, Harrison JH, et al. Successful homotransplantation of human kidney between identical twins. JAMA 1956; 160:277.

2. Murray JE, Merrill JP, Harrison JH. Kidney transplantation between seven pairs of identical twins. Ann Surg 1958; 148: 343.

3. Dossetor JB, MacKinnon KJ, Luck JC, et al. Renal transplantation between identical twins. Lancet 1960; 2:572.

4. Dossetor JB, Morgen RO, Beck JC. Observations on the function of a transplanted kidney. Can J Biochem Physiol 1963; 41:1409.

5. The Relation of Immunology to Tissue Homotransplantation. Ann NY Acad Sci 1955; 59:277.

6. Second Tissue Homotransplantation Conference. Ann NY Acad Sci 1957; 64:725.

7. Dealy JB, Dammin GJ, Murray JE, et al. Total body irradiation in man: tissue pattern observed in attempts to increase receptivity of renal homografts. Ann NY Acad Sci 1960; 87:572.

8. Hamburger J, Vaysse J, Crosnier J, et al. Kidney homotransplantation in man. Ann NY Acad Sci 1962; 99:808.

9. Calne RY, Alexandre GPJ, Murray JE. A study of the effects of drugs in prolonging survival of renal transplants in dogs. Ann NY Acad Sci 1962; 99:743.

10. Murray JE, Merrill JP, Harrison JH, et al. Prolonged survival of human kidney homografts by immunosuppression drug therapy. N Engl J Med 1963; 268:1315.

11. Human Kidney Transplantation Conference. Transplantation 1964; 2:147.

12. Dossetor JB, Gault MH, Oliver JA, et al. Cadaver renal homografts: initial experiences. Can Med Assoc 1964; 91:733.

13. Oh J. Early research towards his PhD (Experimental medicine). McGill University, 1969.

14. Kissmeyer NF, Olsen S, Petersen VP, et al. Hyperacute rejection of kidney allografts associated with pre-existing humoral antibodies against donor cells. Lancet 1966; 2:662.

15. Starzl TE, Marchioro TL, Terasaki PI, et al. Chronic survival after human renal homotransplantation. Ann Surg 1965, 162:749.

16. Starzl TE, Marchioro TL, Farris TD, et al. The problems and prognosis of the chronically surviving patient after renal homotransplantation (Seventh Transplantation Conference). Ann NY Acad Sci 1966; 129:598.

17. Dossetor JB, MacKinnon KJ, Gault MH, et al. Cadaver kidney transplants. Transplantation 1967; 5:844.

18. Taguchi Y, MacKinnon KJ, Dossetor JB. Renal allograft modification by donor antigen in the rat. Evidence for significance of this principle in man. In: Dausset J, Hamburger J, Mathe G, Eds. Advance in Transplantation. Munksgaard, Copenhagen, 1968; 393.

19. Lillehei CW. A personalized history of extracorporeal circulation. Trans Am Soc Artif Inter Organs 1982; 28:5.

20. Terasaki PI, Ed. History of HLA: Ten Recollections. UCLA Tissue Typing Laboratory, Los Angeles, 1990.

CURRICULUM VITAE

John Beamish Dossetor

Born in India in 1925 of Australian parents; educated in England (Marlborough College, Wiltshire) to enter Oxford University (St. John's College) as an Open Scholar in Natural Science in 1943 to study medicine. After three years in Oxford, completed an Honours degree in Physiology before moving in 1947 to St. Bartholomew's Hospital for clinical training leading to medical degrees from Oxford University and London University in 1950.

Postgraduate clinical residency training in London during the next five years was interrupted for two years of National Service in the Royal Army Medical Corps, mostly in the Gurkha Brigade in India, Malaya, and Singapore. Returned to London for residency training at the Royal Post-Graduate Medical School, Hammersmith (Prof. Dame Sheila Sherlock) and at St. Bartholomew's Hospital (Sir Ronald V. Bodley Scott), obtained the MRCP (UK) in 1955 before moving to McGill University (Royal Victoria Hospital) under Prof. R.V. Christie. After years as teaching fellow and then chief resident in Medicine at Royal Victoria Hospital (1956-57), was awarded a Canada Life Insurance Research Fellowship to do research in circadian rhythms of electrolyte excretion and renal function, in normals and patients, leading to Ph.D. at McGill (1961) in Experimental Medicine, following a post-doctoral fellowship of the United States Public Health Service at New York University Medical School (Bellevue Hospital) with Dr. L.G. Wesson.

In 1961 appointed Director, Renal and Urologic Research, Royal Victoria Hospital, Montreal and in charge of the renal service, with responsibility for dialysis and the medical aspects of renal transplantation. (In the mid-sixties the Royal Victoria series of cadaver-donor transplants was the second largest such series in the world.) In 1963, elected Fellow of the American College of Physicians. Between 1961-69, immunological aspects of renal transplantation became the principle research field. In 1968, while at McGill, appointed a Career Investigator of the Medical Research Council of Canada and this appointment is still active. Served on MRC Committees for: a) Grants in aid of research, Immunology and Transplantation; b) MRC multicentre trial of ALG in Canada; c) Committee to revise "Ethics in Human Experimentation" guidelines (1985-87); and d) Human Somatic Cell Research Committee (1988-89).

In 1969, appointed Professor of Medicine, University of Alberta and Director of the Division of Nephrology and Immunology, Department of Medicine. In 1970, appointed Chairman and Co-Director (with Dr. Erwin Diener) of a research group in Transplantation established by MRC, Canada, at the University of Alberta. Studies conducted in HLA immunogenetics, with two groups of Inuit in the Arctic and Hutterite communities in Alberta, as well as in immunologic monitoring of kidney transplant recipients. Elected to Fellowship of the Royal College of Physicians, London, UK, in 1972.

Interest in medical ethics led to being Co-Director of an International Symposium in June 1979 in Edmonton on "Medical Advances through Clinical Trials: a Symposium on Design and Ethics of Human Experimentation" the proceedings of which have been printed. By 1984, a decision was made to change career direction into bioethics and both MRC, Ottawa, and the University approved a sabbatical year for 1985-86. This sabbatical was spent in medical ethics (bioethics) at UCSF, San Francisco; at the Bioethics Center in Montreal;

and at the Hastings Center, New York and culminated in the launching of a Joint-Faculties Bioethics Project at the University of Alberta and the University of Alberta Hospitals. He and his colleagues are responsible for bioethics teaching at all phases of the medical curriculum and for clinical bioethics rounds for residents and nurses at the hospital. In 1990, appointed Director of the newly formed Division of Biomedical Ethics and Humanities, Faculty of Medicine, University of Alberta, and the interdisciplinary bioethics group became the Bioethics Centre. He is Past President of the Canadian Bioethics Society.

Margaret and he were married in 1957 and they have four children: Frances (1957), John and Clare (1959), and Moira (1963).

SOME PERSONAL REFLECTIONS ON THE DEVELOPMENT OF TRANSPLANTATION

Paul S. Russell

Address: Department of Surgery
Harvard Medical School
Massachusetts General Hospital
Boston, Massachusetts 02114

Paul S. Russell

1950

1975

SOME PERSONAL REFLECTIONS ON THE DEVELOPMENT OF TRANSPLANTATION

Paul S. Russell

This account, which is based upon my own involvement in the field of transplantation, will inevitably be a selected set of reflections and recollections. In some respects it will have the flavor of an autobiography, but it is intended mainly to be a personal account, based on one observer's view, of the early growth from very small beginnings of a now extensive field of science and clinical medicine, all within the experience of a single generation.

This field did not originate in a single source or growing point but derived from a coalescence of streams originating from widely separate sources. Some of the earliest stirrings were frankly clinical and often sprang from little more than the pressure on courageous, and sometimes foolhardy, physicians who were unwilling to accept, without a fight, the death or disability for their patients that had always awaited them in the past. This story of early clinical trials with transplanted tissues, combined with the fascinating early history of blood transfusion, goes back a number of years and is a subject worthy of study. A second theme can be discerned in the many efforts to experiment with tumors by transplantation. These stretched over many years and led to some of the most durable insights we have of the biological mechanisms that determine the fate of transplanted tissues. For example, inbred strains of animals were developed in part as an offshoot of work with transplanted tumors. Finally, there is a fairly long but sparse history of direct, laboratory experiments on tissue transplantation using normal tissues. Thus, even though there is some background of experimentation relevant to tissue transplantation going back into time it is quite proper to conclude that the theme of purposeful and systematic research with normal tissues is of relatively recent origin. The subject has now attracted intense interest fed increasingly by concurrent clinical success as well as by the excitement and intellectual stimulation which unfolded as such experiments, initially in a very few laboratories, began to reveal remarkable things full of promise for further progress.

The subject of transplantation first came to my attention when I was looking over some recently published papers late one evening in the Treadwell Library of the Massachusetts General Hospital in the summer of 1953. I had returned from military service during the Korean war a few months before and was hard at work as a surgical resident. During my medical school years in Chicago I had learned some rudiments of research in the laboratory of Charles Huggins, a thoroughly inspiring man, who was mainly interested in the responsiveness of cancers to hormonal changes. By 1953, some five years after graduation from medical school, I had begun to feel a strong yearning to explore a new field of research, but I don't think I placed first importance on whether or not it was a field that could take a practical turn.

At about that time some initial interest in kidney transplantation was awakening at the Peter Bent Brigham Hospital on the other side of Boston, but I was quite unaware of this and had only visited the Brigham once when I took my internship examinations there in 1947. That night I came across the now famous little paper by Billingham, Brent, and Medawar in *Nature* in which their discovery of "actively acquired tolerance" of skin grafts in mice was described. I had read the thorough accounts of the behavior of kidney transplants between dogs, which had been produced quite independently by Dempster and by Simonsen and had been impressed by the apparently inexorable and decisive character of the rejection response. But not until I became aware of the dazzling finding of tolerance did the field begin to seem truly appealing as an area full of opportunity.

I went to my Chief, Dr. E. D. Churchill, and told him of my new quest saying that I would like to apply to work in Medawar's laboratory at University College in London. Not having heard of Medawar or of the field of transplantation he expressed only mild interest but told me I could try my luck and that he would release me for a year or so if I were successful.

Peter Medawar's reply of April 3, 1954, was a cheerful and kindly turn down. He explained, "This is an undergraduate teaching department of zoology: our research interests are in paleontology (particularly of triassic reptilian fauna), in parthenogenetic fish, in conditioned reflexes in sea anemones, the taxonomy and ecology of lugworms - and, of course in skin transplantation, a subject on which a little group of four of us work. I've already turned down rather a number of requests from native and foreign scientists to come and work here." He suggested that I might find a place in the surgical laboratories at the Hammersmith Hospital under Professor Ian Aird.

Somehow this reply, far from making his department of zoology seem distant and irrelevant from what I should be learning, only made it even more attractive. Looking back, I now realize that several of the subjects he described eventually turned out to have special interest for me at one time or another. I returned to seek more active help from Churchill which he promptly gave me. His letter to Medawar must have been a good one, and a personal plug from my English surgical friend Athol Riddell, then at University College, unquestionably helped also. It was Riddell's team in Bristol, incidentally, which was later to be the first to observe that liver transplants between certain pigs could be accepted even when transplants of other tissues were not. This finding was later exploited very effectively by Roy Calne and colleagues. At any rate I promptly received another nice letter from University College saying that it might be possible to fit me in after all. I was to begin in September of 1954 as the first foreign "visitor" the laboratory had ever had.

Transplantation Research at University College, London
1954 to 1955

Medawar was then 39 years old and I ten years his junior. His laboratory group consisted of Rupert Billingham, with whom he had collaborated since their days at Oxford before they had both moved on to Birmingham; Leslie Brent, a recent PhD graduate who had received his degree under Peter at Birmingham; and Elizabeth Sparrow, another holder of the PhD degree. My first encounter with Peter Medawar was memorable. As he rose from the desk in his small office to greet me, his large size was immediately impressive. This quality was all the more striking as it was combined with an almost fearsome, though warmly human, intelligence which was set off by the dark good looks of a film star. He fixed his large, bright eyes upon me, welcomed me cordially and asked some questions about the plans that my wife and I had for settling in London. The settling-in actually proved to be quite important for us since my wife, Allene, was to deliver our first child only five days later, somewhat earlier than expected.

Having established that I came with no pressing or specific research objectives of my own he passed me a single sheet of paper on which he had typewritten outlines for three series of experiments, one to be carried out with Billingham, one with Elizabeth Sparrow, and one with him. He then said, "We have good talk here in the department, but we don't talk politics." This remark, I later learned, was important as a number of the more distinguished members of the Department were active in the British Communist Party and Peter was justifiably worried that a naive, young American surgeon, fresh from a country torn by "McCarthyism," might make the lively and pleasant conversation at tea time into an ugly political free-for-all. As it happened I was captivated by the gruff pronouncements of J.B.S. Haldane, the urbane charm of David Newth, and generally found my new world completely absorbing.

Most of my new colleagues were fascinating to me because of the broad range of their interests. Among those often present for afternoon tea, in addition to Medawar's own group and those just mentioned above, were such people as John Maynard Smith, one of Haldane's inner apostles of numerative population genetics, Richard Freeman, Alex Comfort, gerontologist and later salesman for sexual freedom, D.M.S. Watson, Medawar's predecessor, G.P. Wells, son of H.G. and, it turned out, the expert on lugworms, Kenneth Kermack, Brian Boycott, and a number of others, each major intellects in their own lines of fundamental biology. And I should not forget Helen Spurway, Haldane's wife, whose interest in a certain species of fish, which she suspected of reproducing parthenogenetically, added a good deal of spice to many discussions. It was in this environment that my scientific education was to begin in earnest.

Each of Medawar's immediate colleagues was given a small room in which to work. The room served as a laboratory, study, office, and all-purpose meeting place. Each room contained a cabinet to hold a few small surgical instruments, some anesthetics, sterilizing solutions and the like. Microscopes were probably the most expensive item of standard equipment and anything more elaborate, such as a calculating machine, was the common property of the department.

At that time the work was strikingly simple compared to what one has come to expect in a modern immunology laboratory. Almost all experiments were carried out using whole animals. When I was in the group it was rabbits and mice only. A few strains of inbred mice were available and these were very carefully maintained by Leslie Brent who personally selected animals for breeding and maintained their pedigrees. The animals were housed in a few rooms constructed under the eaves of the old building fixed up for Medawar's group, after considerable discussion, before its move from Birmingham.

My schedule called for one or more half working days each week with my preceptors. With Billingham, a study of the striking phenomenon of wound contraction using large, full-thickness cutaneous wounds in the rabbit was begun; with Elizabeth Sparrow the plan was to learn something more about the hormonal control of pigmentation in the skin of mice; and with Medawar, himself, I was to explore the behavior of transplanted adrenal glands between inbred strains of mice.

Initially, I spent a lot of time in the library reading all I could about any past work which might prove to be relevant to our undertakings. I read almost every paper produced by any member of the group and found much to learn from Medawar's own writings. Their clarity, grace, and occasionally, their irreverence and humor gave me a completely new concept of what scientific writing could be. I began to see how one's sense of the value of ideas and of their place in the structure of civilized thought can be expanded in the light of a broad understanding of literature and history. This was why I soaked up the teatime talk of someone like Kenneth Kermack, a paleontologist, who could expound convincingly on the detailed operation of Greek triremes. Someone less naive than I might have dismissed all this as pure eccentric pedantry, but for me it was pure pleasure. Although there were occasional seminars on various topics in the department the subject of transplantation was such a parochial one with us that few others cared very much about it. We did see Jim Gowans and Avrion Mitchison from time to time, and I can remember some particularly exciting conversations involving them which played over the biology of immune reactivity as it was then understood.

I was also privileged to go to a few meetings devoted to quite different scientific matters. I remember especially one meeting of "The Bone and Tooth Society" presided over by the venerable Sir Edward Mellanby, discoverer of vitamin D, at which several experiments in animals having to do with mineral balance were discussed. Concern was expressed that these experiments, although quite reasonable and feasible from a scientific point of view, might be delayed by the Home Office's animal welfare division in view of the very tight regulations which were in effect even then in Britain. Mellanby said something like, "It's far easier in this country to experiment with men than animals, and preferably with oneself." This was a surprising statement to me, but it confirmed my impression that a certain tendency toward self experimentation had grown up in Britain. This was exemplified especially by Haldane and his father J.S. Haldane, who had used themselves for important, and sometimes dangerous, physiological experiments during wartime.

Life was also enriched by social activities with colleagues. The "Marlborough Arms," a pub in the Gower street area near University College, was a favorite refuge for those seeking a break from the laboratory. Leslie was a master at bar billiards, and Peter was pretty good at the game, too. It was in front of this landmark that Helen Spurway had what became a famous altercation with the London constabulary which ended up in her spending a brief period behind bars.

The experiments in our laboratory began to go well. Billingham and I devised what turned out to be a highly reproducible quantitative system for the serial evaluation of wound contraction in the rabbit. We established the pace of the process and then went on to explore the effects of certain variables on it. Cortisone would greatly retard wound contraction. Old age slowed it appreciably. The shape of the original wound also played a part in determining how the wound would close. We wanted especially to determine whether there was any evidence that a prior wound in a distant location from the test wound would accelerate any measurable component of healing, but we could find no support for this ancient idea. We concluded that any stimulatory substances involved in the movement or division of cells as part of the healing process must exert their effects locally (1).

Billingham was a delight to work with. His sense of humor became legendary, and he always seemed to see the amusing side of things. His great abilities were at their peak in his practical approach to research. He was marvelous at designing new techniques and at tinkering. As I like all these things, too, we got along very well.

My efforts with Elizabeth Sparrow to link certain aspects of pigmentation in the mouse with various hormonal changes were less successful. In the process, however, I taught myself how to do hypophysectomies in mice and learned a number of other techniques which were fun to know. I enjoyed working with Elizabeth also and was very pleased when she was able, later on, to come to Boston and help with the establishment of our laboratory.

With Medawar, himself, our objective became to learn whether adrenal cortical allografts behaved in the same manner as skin grafts under standardized genetic conditions. There had been much in the literature about the apparent "privilege" of endocrine transplants and about their dependance for survival on a deficiency of the appropriate secretion in their recipients. The technique we worked out made use of tiny "shavings" of donor strain adrenal cortex which were implanted as free grafts in various recipient sites. It was a new challenge at that time, but one which is still familiar, to determine the status of such invisible grafts buried out of sight in a recipient. This could be done only by functional tests or by histological examination of grafts excised at selected times after transplantation.

As our murine recipients had been adrenalectomized before receiving their adrenal grafts they had to be supported by injections of a deoxycorticosteroid preparation until the grafted adrenal tissue could become functional. Thereafter we assessed the function of the transplants by the survival of recipients placed on a very low salt diet. It turned out that these particular endocrine grafts behaved very much like skin grafts in every respect as recipients of allografts (then still called "homografts") would die quite promptly when challenged with a low salt diet ten days or more after transplantation. It was gratifying to see similar animals survive beautifully when the adrenal grafts were transferred to mice that had been rendered specifically tolerant of donor strain spleen cells by neonatal intravenous injection according to the method that had just been devised by Billingham and Brent. Furthermore they rapidly succumbed when tolerance was abrogated by the transfer to these recipients of normal spleen cells of the recipient strain or, more rapidly, if these cells had come from mice which had previously been sensitized to donor cells. Peter enjoyed calling this "immunological adrenalectomy" (2).

It was, incidentally, in this connection that I first heard the word "sensitized" in connection with a state of immunity rather than "immunized." It became a convention later on to use this word when referring to transplantation-induced immunity, a convention which we later applied to patients who showed evidence of previous exposure to histocompatibility antigens by serological reactivity in vitro. Such serological reactivity was, of course, very difficult to demonstrate for a long time. And even after Peter Gorer had shown its presence in certain mice to cells from transplanted tumors that they had rejected it was not easy to do likewise for the recipients of grafts of normal tissues (3). Furthermore, repeated attempts to transfer sensitivity to recipients from demonstrably sensitized animals failed (4). Only much later did our team in Boston, headed in this instance by Henry Winn, show that skin grafts, and indeed grafts of a variety of other tissues, could be destroyed within hours by the injection of a sufficient dose of an appropriate antiserum (5). The exact degree of involvement of various classes of antibodies against antigens represented on transplanted tissues in the rejection response, at different stages after transplantation and in the presence of different kinds of immunosuppression, remains undetermined.

My happy and productive fifteen months in London came to an end too soon for me. I had made some lifelong friends, had learned a vast amount both in the laboratory and elsewhere, and returned with an entirely new vista for the future. Although I had been the first foreigner in the laboratory, a number of others came later and all made substantial contributions to the field. William Hildemann arrived the next year and Paul Terasaki the year after. Both became good friends. I learned later that Julian Huxley, to whom I had been introduced by Peter, had moved into my little room in the department. Throughout our time in London, Peter and Jean Medawar were extremely thoughtful and gracious toward us. We came to know all of their children and enjoyed many evenings together. Peter sensed my Anglophilia and rightly concluded that a taste of some of the more traditional extensions of British science would enrich my experience and add to the indelible memories I was accumulating. The Royal Society meetings were especially fine for this purpose, both in quality and flavor, and the Royal Society Dining Club was a particular treat.

After returning to Boston it was first necessary to complete my prescribed postgraduate training in surgery. This went along well in the demanding environment so familiar to young surgeons, and I finished my chief residency in December of 1956.

Starting Transplantation Research at Massachusetts General Hospital, 1957 to 1960

Dr. Churchill invited me to remain as a junior staff member. In a clinical department such as ours the duties of a young clinician are numerous, usually including significant responsibility for patients and for teaching. Saving time for research was a challenge. Nevertheless, laboratory research was encouraged, and I was determined to do some. I shared a small laboratory with a capable surgical colleague, Dr. Hermes Grillo, in what had been a storeroom in the Huntington cancer research laboratories, which were under the direction of Dr. Paul C. Zamecnik. Mary Wood joined me as my first technician shortly after her graduation from the University of Indiana.

We set out to study parathyroid transplantation and a few other more fundamental questions of current interest including the nature of the antigenic stimulus emitting from tissue transplants. Was it cellular or subcellular? Our system for looking at this question was a simple one. It consisted of testing the degree of sensitization which could be produced in a rabbit by receiving a subcutaneous implant of living epidermal cells housed in a cell impermeable chamber. By this time Elizabeth Sparrow had joined us for two years from London and a welcome addition she was. She did much of the work with the chambers which eventually gave a scatter of results in that the test skin grafts from the paired donor rabbits placed onto recipients bearing chambers containing living epidermal cells from these donors were sometimes rejected in accelerated fashion and sometimes significantly later than control grafts. We never published these results as we didn't know how to interpret them. As I look over my old laboratory notebooks I can find a number of experiments, like these, which somehow never came to anything. Several of them still strike me as founded on pretty good ideas.

Our first research fellow, a bright Harvard medical student by the name of Ruben F. Gittes, came to work in the laboratory. He did most of the parathyroid work and showed the persistence and imagination which has continued in his subsequent career. We thought we had to use rats for these experiments as something was already known about the anatomy of the tiny parathyroid glands in the rat, and we expected that the removal and transplantation of such structures would be hard enough even in the rat. We did not have access to the few inbred strains which were being developed and had to do all our work with relatively heterogeneous animals. Nevertheless, the parathyroid transplant system offered considerable attraction for us because we were able to follow the function even of a single gland only a millimeter in diameter, transplanted to a parathyroidectomized recipient, with blood calcium levels. Some of the experiments called for the serial transplantation of different tissues of the same genotype so we carefully nurtured all of our transplant pairs for repeated use. The results of the experiments with rats showed a most interesting capacity of parathyroid tissue to survive when transplanted between animals which would have rejected skin grafts very promptly. Furthermore, some parathyroid transplants even outlasted two skin grafts from their appropriate donors placed one after another on the same recipient. In other donor-recipient combinations of animals, acute rejection of long-surviving transplants was brought about by the rejection of donor skin grafts placed after months of gland transplant survival.

These findings have not been reexplored in the light of present day knowledge, but I suppose one possibility is that this glandular tissue is relatively sparsely populated with dendritic cells and that they have a tendency to diminish in number even further after grafting. If this were true it would mean that parathyroid tissue, at least in the rat, could be less immunogenic than some other tissues in the rat and that even this level of immunogenicity might diminish further with residence in an allogeneic recipient as those antigen-presenting cells present migrate away.

When it came time to publish our findings with respect to parathyroid transplantation in the rat, I learned something else which has stayed with me. The principal editor of the *Journal of Experimental Medicine* was the grand old gentleman and superb scientist, Peyton Rous, who later shared the Nobel prize with my first teacher, Charles Huggins. Dr. Rous sent our paper back with a long, friendly letter containing detailed criticisms. He suggested, for example, that I remove my reference to "humans," saying that one should never refer to our species other than as "human beings." This reinforced my conviction, gained from reading Medawar's papers, that proper scientific writing is a demanding and exacting business, often imperfectly practiced. After we had worked on it a bit more he accepted the paper for publication (6).

As we believed from our rat work that there might be a qualitative deficiency in the expression of histocompatibility antigens on parathyroid cells, and that the presence of Y chromosome-determined antigen(s) could be tested best with mice, we miniaturized our techniques further for use in mice. We found no evidence, however, that histocompatibility antigens determined at the Y chromosome were not well represented in their parathyroid tissue (7).

During this period I became involved in two experimental efforts to apply transplantation to clinical problems. The first took advantage of the remarkable phenomenon of temporary, complete morphological remission of acute lymphatic leukemia which could be accomplished with chemotherapy in many children suffering from this rather common form of that disorder. A pediatric hematologist, Dr. Joseph McGovern, and I devised a treatment plan which depended upon whole body irradiation in the lethal range after recurrence of the disease had taken place. The plan was to remove a sufficient number of normal-appearing bone marrow cells from our patients during the phase of remission to rescue them after they had received this lethal, but also therapeutic, dose of irradiation. A lot had to be done to make this trial possible. We had to work out the techniques for removing and storing the marrow (Dr. Leonard Atkins was invaluable in the storage effort), and we had to figure out how to administer whole body irradiation with equipment poorly suited to the task (Dr. Edwin Webster contributed here). We treated six patients and clearly helped at least two of them (8). One little girl I remember especially. Although in a desperate and terminal state with all the distressing complications of raging leukemia, she was restored to seemingly perfect health for about a year after our cumbersome treatment before succumbing to complications from a blood transfusion. The principle of autologous bone marrow transplantation as protection to permit toxic cancer treatments has endured.

The other project was not a success. We had concluded from our parathyroid transplant work in the rat that transplanted parathyroid tissue, at least in that species, could survive better than grafted skin. We had also delineated the conditions of freezing and thawing in the presence of glycerol or dimethylsulfoxide which would allow reliable storage of parathyroid tissue for prolonged periods (9). The thought was to collect a number of small samples of benign parathyroid adenomas, freeze them, and then, after thawing, place them as free grafts in the rectus muscles of patients who had become profoundly deficient in parathyroid secretions for one reason or another. There were clearly several possible reasons why the two patients who bravely agreed to this approach enjoyed no measurable benefit. Nevertheless, the idea of offering a range of donor tissue, smorgasbord style, to the immune system of a recipient still has its charms for me, at least in the state of ignorance in which we then found ourselves.

At about this time I received a letter from Dr. George H. Humphreys, Chairman of the Department of Surgery at Columbia University's College of Physicians and Surgeons. He stated that he would like to come to Boston to speak to me about joining his department. Not long thereafter arrangements were made for my wife and, by that time, three small children to move to New York where I was to become an Associate Professor and take charge of their research laboratories.

Columbia University, College of Physicians and Surgeons, 1960 to 1962

I had a marvelous time at Columbia and retain the warmest feelings for that huge, valuable and beleaguered institution. Mary Wood and I were given two large rooms on the fifteenth floor of the cavernous building which was then the center of medical school activities. Housing for our animals was an important part of our needs and we were fortunate that we were able to keep some of them in a small room down the hallway from our main laboratory. By this time we were maintaining several strains of inbred mice, which we had received from a number of sources. I well remember the move of all of our live animals and laboratory gear in a large truck from Boston to New York one hot spring day. We also brought along our tank of liquid nitrogen containing frozen rat parathyroids which were to be replaced in their donors, bouncing along in another part of the truck, after a prescribed period of preservation. It was quite an effort.

I was especially fortunate in having the collaboration from the beginning of two young surgical residents whom George Humphreys had sent in my direction, Jim Chandler and Richard Simmons. Dick Simmons and I had a particularly good time. I suggested to him that we might study the transplantation biology of the placenta using some of our strains of inbred mice. Dick fell to work on this project with what I found to be his characteristic intensity and intelligence. We were able to show for the first time that murine placental tissue at about 17 days of gestation defied rejection completely when transferred to an adult allogeneic recipient even when the recipient in question had been powerfully immunized by prior exposure to antigens known to be expressed in the conceptus of which it was a part. This suggested that the usually expected histocompatibility antigens were somehow not expressed in the normal fashion on trophoblastic cells (10). This conclusion was, perhaps, somewhat reminiscent of our previous parathyroid work although we had not found that any glandular tissue we had tested seemed to be completely devoid of the ability to provoke a rejection response. Thus, this was a somewhat startling conclusion as it was generally believed that all of the nucleated cells of an individual expressed these antigens at least to some degree. Indeed this conclusion had been supported by the work that Medawar and I had done, as far as it had gone, in comparing adrenal, skin, and spleen cells. This was some time before the great array of differentiation antigens, even the T and B antigens, had been discovered on lymphoid cells and long before the subtleties of cytokine regulation of antigen expression on some cells had been revealed. With another resident, William Healey, we became interested in the histocompatibility relationships among members of families of turkeys which included parthenogenic offspring. Bill had read in the *New York Times* that a small number of these curious parthenogenic birds had been produced at the research facility of the United States Department of Agriculture in Beltsville, Maryland. The process was apparently encouraged by certain virus infections in the mothers of the parthenogens, but somehow it indeed seemed to take place as their authenticity was strongly attested to by those in charge. We went to Beltsville, devised satisfactory techniques for the transplantation of skin between turkeys, and soon produced results which were entirely consistent with the interpretation that these full-grown turkeys, all female, were the parthenogenic offspring of their mothers. All skin grafts from mothers to parthenogens were rejected while all grafts in the reverse direction were permanently accepted (11).

Another subject of research at that time was the graft-versus-host disease that Billingham and Brent had described in certain of their mice neonatally injected with allogeneic spleen cells from adult donors. Billingham called the resultant condition in these mice "runt disease." One of my purposes here was to elucidate the extent of reversibility of the effects of injecting various doses of dissociated spleen cells intravenously within hours of birth. Some of these experiments required that a second dose of spleen cells, this time derived from adult members of the same strain as the newborn mouse itself, be delivered at selected times a few days later. These were technically demanding experiments and often required that injections be given at odd times including weekends. As things were quiet in the laboratory at those times I often took one of my children in to help hold the minute, pale, hairless baby mice just right to receive their intravenous injections in the orbital vein or sagittal sinus.

This work was later presented at one of the most pleasant and informative meetings I have ever attended (12). It was a Ciba Foundation Symposium. Generations of workers in the biological sciences have now become accustomed to the quiet gentility of Ciba House in London and to the high degree of professionalism with which their intimate meetings are conducted. Every utterance by the small group of invited participants is duly recorded and made a part of the published volume which promptly appears after each meeting. On this occasion the meeting was held at Apothecaries' Hall in the City of London rather than in the foundation's own building which was being renovated. It seemed especially remarkable that in this ancient place, glowing with elegance, we should be treated to the first report by Jacques Miller of his spectacular findings in association with neonatal thymectomy in the mouse.

A number of other meetings of the still small community of people interested in transplantation also served to make life all the more stimulating and enjoyable. The famous congresses on transplantation, organized under the aegis of the New York Academy of Sciences by John Converse and Blair Rogers later joined by the resourceful Felix Rapaport, were high points. The first of these conferences was held in January of 1955. They offered marvelous opportunities to meet virtually everyone active in the field, and one could pretty well follow all their work since these were biennial occasions.

I can remember many presentations at these meetings with especial clarity. One of the most impressive was Jim Gowans' paper, given in the ballroom of the Barbizon Plaza Hotel in New York, in which he proved that small lymphocytes, on transfer to histoincompatible recipients, will transform to blast cells with undeniable immunological activity in vivo, thus establishing a major property of these cells (13). It was a typically airtight argument in which no controls were omitted. Everything had been repeated an extra time, and in all respects the demands of scientific rigor had been squarely met. He finished to a standing ovation.

Good as these meetings were, there was increasing dissatisfaction, mainly from the growing numbers of European workers in the field. They understandably felt that meetings should be held alternatively in the east and west. An interesting series of events followed which culminated in the foundation of the Transplantation Society in February of 1966 as a direct offshoot of the New York Academy meetings. Bernard Amos, one of Gorer's graduates who by that time had become a professor at Duke, played a pivotal role in the foundation of the new society through his wise and timely leadership.

I had every reason to settle in permanently at Columbia. My position held academic tenure; my colleagues were stimulating, and the clinical work and departmental responsibilities were all interesting. Furthermore, George Humphreys was a wise, supportive, and respected leader. Not only was I able to attend seminars and discussions at Columbia organized by Elvin Kabat, but I was also welcomed by the group at New York University which included Lewis Thomas, Baruj Benacerraf, Jeanette Thorbecke, H. Sherwood Lawrence, and others. My main contact with the NYU group was by attending their Thursday immunology luncheons, marvelous occasions. Still, when the invitation came from Harvard and the Massachusetts General Hospital to return to succeed E.D. Churchill there seemed to be no alternative but to accept. Thus, in the spring of 1962 we returned to Boston after only two fruitful years in New York.

Further Developments in Transplantation at the Massachusetts General Hospital, 1962-

This segment of recollections is clearly the longest and the most complex. Accordingly it must be even more selective than the rest, confining itself simply to a few of those things which might be of interest to a present-day student of transplantation.

By this time interest in the field of clinical transplantation had awakened in steadily more institutions, almost all of them in the United States, France, or Britain. There was excellent experimental work going on in the Netherlands, Israel, and in Sweden and Denmark, and the brilliant group under Macfarlane Burnet in Melbourne was producing ideas and experimental results which were widely respected. Although clinical transplantation was confined to a mere handful of places, this was about to change. This could be attributed mainly to the emergence of azathioprine (Imuran) as a chemical immunosuppressant.

As is well known, George Hitchings and Gertrude Elion had synthesized this analogue of 6-mercaptopurine (6-MP) as part of a systematic effort to discover a compound which would compare favorably with 6-MP, which had known immunosuppressive properties. The striking results of Robert Schwartz and William Dameshek (14), who had found that 6-MP treatment, when given along with human serum albumin to rabbits, would result in subsequent nonreactivity of these animals to later challenges with the same antigen, had also heightened attention to purine analogues, which had long been a special interest at Burroughs Wellcome. Roy Calne had found that azathioprine was impressively effective in prolonging the survival of kidneys transplanted between dogs, a finding on which he expanded during a period of fellowship with Joe Murray at the Brigham Hospital. The stage was thus set for clinical trials, and they soon showed promise.

My return to Boston had, by chance, coincided closely with these events. The time seemed to have come for transplantation of the kidney to be tried more widely, and I decided to go ahead with such trials at the Massachusetts General. I was further encouraged by the results which were pouring forth from the pioneering transplant programs at the Medical College of Virginia under David Hume, who had moved there from the Brigham not long before, and from Denver, where Tom Starzl and Bill Waddell already had shown some especially interesting things. For me the most important and surprising thing, which I learned first from the Denver experience, was that acute rejection of the transplanted kidney could actually be reversed by increasing the dosage of a cortisone derivative. None of the experimental work up to this time had really fastened adequately on this matter of the reversibility of rejection reactions and almost all the rejection reactions I had seen in experimental animals looked pretty irreversible. The potency of the corticosteroids in prolonging the survival of transplanted tissues in animals had been described quite well by Peter Krohn in England (15), working in association with Medawar, and the earliest clue that these agents might be helpful in kidney transplantation in patients came from Willard Goodwin in Los Angeles. When the steroids were combined with azathioprine, however, attention shifted to chemical immunosuppression leaving behind the distressing side effects of whole body irradiation.

We began kidney transplantation on April 24, 1963. In the earliest days all of the donors were, of course, from living relatives of the patient, although some kidneys had been utilized at the Brigham following their removal in connection with certain neurosurgical procedures (to drain cerebrospinal fluid into the urinary tract) or for other reasons. I visited the Peter Bent Brigham Hospital and watched Joe Murray do a kidney transplant. Joe was most kind and helpful in every way and has always been so ever since.

Fearing infection in our immunocompromised patients we wrongly thought we should place them in the "isolation" ward of the hospital where they must have been exposed to more organisms than otherwise. Fortunately we did have the early postoperative patients in a separate room where we watched the profound, and uncontrolled uremia from which they suffered melt away as the new kidney began to function. Every detail of patient management had to be worked out anew. The question of isolation for patients, mentioned above, is an example. A few years later, when I visited Christiaan Barnard in Capetown, I was impressed to find the most elaborate isolation facilities imaginable. Special clothing, head to toe, was provided for everyone entering the patient's room; the food was sterilized before being passed through a port into the room and bacteriological monitoring was strict. Only gradually did we come to realize that it is mainly the airborne pathogens which must be denied access to immunosuppressed patients. Thus, our current approach, on the advice of Robert Rubin, is to maintain patients on high-dose immunosuppression in rooms served by highly filtered air delivered under constant positive pressure.

This leads me to mention another point of importance which we learned in the early days. It is the importance of teamwork. A stable group of committed people representing several conventional disciplines is essential for good results. For kidney transplantation the group must include appropriate physicians, ie, nephrologists, a psychiatrist, infectious diseases experts, strong nursing, dietary experts, and, for certain purposes, others. It worried me that financial concerns could creep into patient management decisions when a team of people is involved. At that time there was considerable open competition in the minds of both physicians and patients between the relative merits of dialysis versus transplantation treatment. Accordingly we established a formal group practice for the care of all of our patients, which had come to include dialysis patients as well, since we had been obliged to start up a dialysis unit for them. This expedient has served all concerned very well and has helped to give coherence to our growing group. As additional organs were added to those we felt capable of transplanting, appropriate people were added to the group. The possibility of organizing ourselves in this way, which we owed to the higher ups in our institution, was one of the most helpful things encountered along the way, a way which was not always free from obstacles.

One respect in which our institution did not choose to support us was in the field of heart transplantation. The story is much too long to be recounted here, but the decision of the Massachusetts General's Board of Trustees to suppress heart transplantation because of its feared potential to coopt resources and the sense, very widely held at the time, that it represented a high water mark for highly technical interventions of an "extreme and expensive" sort which should not be condoned, was a disappointment. This judgment has since been reversed.

I have been very fortunate in my clinical colleagues. Although they have been too numerous to name in full, I should mention Lot Page, George Baker, Clyde Beck, and for many years, Nina Rubin as nephrologists, with John Herrin as pediatric nephrologist. In infection control K. Frank Austen and Robert Rubin have been strong contributors. Hepatologists have been Jules Dienstag and William Katkov. Psychiatrists have included Joseph Lipinsky and Owen Surman. Urologists have been Wyland and Guy Leadbetter followed by Hugh Young. The surgery of transplantation has become something of a speciality. None of the surgeons who served in our group from time to time had any background in transplantation so we all learned together as we went and as we took on new organs to transplant.

The principle surgeons at the staff level have been Anthony P. Monaco, Benjamin A. Barnes, Robert J. Corry, A. Benedict Cosimi, Francis L. Delmonico, and Hugh Auchincloss Jr., with people devoted to cardiac and pulmonary surgery taking on heart and lung transplantation more recently in association with the larger group (Gus Vlahakes for the heart and John Wain for the lungs). The subject of teamwork and cooperation suggests that mention be made of two interesting examples of this which we have witnessed in Boston and which are of special importance to the clinical application of knowledge in the transplantation field. The first of these was the establishment of a system for the sharing of organs for transplantation, first in the Boston area (as the "Boston Interhospital Organ Bank") and later throughout New England (as the "New England Organ Bank").

The concept for this organization originated one Sunday morning in the mid-1960s when my colleague Francis D. Moore, Chief of Surgery at the Peter Bent Brigham Hospital, called me at home to say that he had heard on the radio of a patient recently admitted to the Massachusetts General who might prove to be a perfect donor of a liver for one of his patients. I remember this patient well. He was a courageous policeman who had been shot in the head while trying to stop a robbery. The concept of "brain death" had been described in detail shortly before by a "Harvard Committee on Brain Death," but legislation to sanction the removal of organs before the cessation of cardiopulmonary function was not yet available. When I spoke to the patient's stalwart wife she understood the opportunity that she and her husband were presented with and she agreed to our removing his liver after death had been declared and transporting it to the Brigham for the first liver transplant to be done in New England. Tony Monaco was instrumental in accomplishing this. From that experience it became plain that hospitals would develop a responsibility to one another for organ sharing. Accordingly, Joe Murray, Frannie Moore, and I gathered together the few people in Boston who were then interested in the subject and set up one of the first free-standing organ exchange organizations with Benjamin Barnes as its Executive Secretary and me as the Chairman of the Board. We have learned a great deal about the inevitably complex process of organ donation and distribution since. Service on the national Task Force on Organ Transplantation later revealed even broader challenges to me, although the principles are the same. It seems clear that such a system can only function if all the parties concerned have a strong sense of responsibility to the group as a whole and understand the need for conforming to its accepted rules, painful as that can sometimes be.

Another example of interinstitutional cooperation I have encountered has been our establishment of "Consortia" for the transplantation of livers, hearts, and lungs in our area. The story of how these came about and a description of the details of their functioning are instructive and interesting but are beyond the scope of this account. Experience with this mechanism has taught us that there can be considerable value in fostering a cooperative atmosphere in a medically active region such as ours. The establishment of uniform criteria for the acceptance of recipient patients, for the management of donors, and even for certain fiscal matters can be helpful to patients, and frequent discussion of clinical experiences and the sharing of operative surgical duties in respect of donors, and sometimes with recipients as well, has been useful to medical teams. Further cooperation for a number of purposes can be foreseen.

One of these, it seems to me, is emerging with the discovery of more and more attractive agents with immunosuppressive properties. Trials of these agents, especially properly planned comparisons of treatment protocols with several agents in each treated group of patients, will be beyond the capacity of a single institution to achieve over a convenient period of time. This means that institutions will have to work out ways of devising and carrying out necessary studies together for the benefit of all. Some of our existing cooperative arrangements may serve as helpful beginnings for such efforts.

I would like to return now to the early history of our transplantation effort at the Massachusetts General. Our group has been strongly committed to maintaining a program of research broadly related to transplantation biology from the very beginning, and this commitment to research has steadily grown through the years. In the mid-1960s Henry Winn, PhD, joined us from the Jackson Laboratory in Bar Harbor. Henry was already a well known expert in immunogenetics, knew much about various mouse strains, and had done interesting work regarding the participation of humoral antibodies in transplant rejection reactions including work in immunological enhancement with George Snell and Nathan Kaliss. Almost nothing was known then about the presence of humoral antibodies against donor antigenic specificities in patients who had been transplant recipients and Henry was well equipped to investigate this area among other things. This he proceeded to do with Michel Jeannet, who was with us as a research fellow, showing that such antibody was often detectable in our patients and that its presence seemed to correlate with the presence of the vascular stenotic lesions which are still such a significant problem in many transplanted organs (16). He also set up the first tissue typing laboratory in New England.

I had become increasingly interested in histocompatibility testing since the response of patients to transplanted organs was so unpredictably variable. Serological reactions being explored at the time included agglutination reactions, such as the one which Jean Dausset was using, and others such as the complement-dependent cytotoxic reaction popularized in the United States by Bernard Amos and later perfected and miniaturized by Paul Terasaki. A few interesting sera with known specificities were available through our friends in the field, but I can remember several evenings when Henry and I spoke to women's groups about the potential importance of tissue typing and then lined up volunteers in our hostess' kitchen to collect blood for Henry's growing serum panel. Some of the sera we collected are still interesting to Thomas Fuller, PhD, who now runs our tissue typing laboratory after a postdoctoral period in Henry Winn's laboratory. Another approach we took to histocompatibility testing was to adapt Medawar's "normal lymphocyte transfer test" to human beings. The vigor of the intracutaneous graft-versus-host response generated by a standard number of living peripheral blood lymphocytes proved to correlate pretty well with the survival time of a small test skin graft transferred later from the recipient of the cell inoculum to its donor. These were days before intense scrutiny of human trials had begun. Nevertheless, we took the greatest care over studies of this kind (and later on with such trials as our use of volunteers to receive test doses of our homemade antilymphocyte serum), and I am pleased to be able to note that no untoward consequences came to any of our subjects.

Henry and I were active members of the Committee on Transplantation, which had been formed under the chairmanship of E. J. Eichwald at the National Academy of Sciences/National Research Council in Washington. Under the aegis of this group, and with the valuable collaboration of Bernard Amos, we organized in 1964 the first meeting on "Histocompatibility Testing" ever held (17). I chose the term "testing" instead of the alternative "typing" because we were still much involved in various biological tests such as our lymphocyte transfer test and we wanted to cast our net a little more widely than simply including serological reactions. This meeting was quite a success and was followed by a laboratory "workshop" organized by Amos at Duke to permit the direct comparison of sera and of methods by a number of investigators. These meetings have now been repeated many times as the number of specificities identified has grown and the chemical structure of various epitopes has been defined. The taxing business of nomenclature was an inevitable task which is still far from complete. Many of us met frequently, as well, in connection with the study section system of research grant review at the National Institutes of Health. Immunologically oriented proposals were reviewed by a large study section devoted to all of "Allergy and Immunology," which was chaired, when I joined it, by H.S. Lawrence. It soon split into two sections (A and B), one devoted especially to immunochemistry and the other to more broadly biological matters. When I later became chairman of the B section we decided to rename it "Immunobiology," and so it remains. The members of this group were highly instructive colleagues. They included: Niels Jerne, Frank Dixon, Robert Good, Ted Boyce, Byron Waksman, Jim Hirsch, Willys Silvers, Frank Adler, Paul Van Arsdel, and Bill Hildemann among others. In later years it has always been worth the considerable effort to participate in various review processes of the NIH. For me these have also included institute-based committees of the National Institute of Allergy and Infectious Diseases and of the National Heart Institute as well as a number of ad hoc bodies for special purposes.

Another major line of investigation which we entered in the mid-1960s was the study of the immunosuppressive properties of heterologous antisera prepared against lymphoid cells. I was aware of the results that Michael Woodruff had achieved in some experiments in rats which were undergoing thoracic duct drainage. He had found that the addition of a few injections of an antiserum made in rabbits against rat lymph node cells would result in a modest increase in the extended survival of skin allografts otherwise produced by thoracic duct drainage alone (18). Subsequently J.H. Sacks, working with David Hume, had also investigated the immunosuppressive effects of such sera and found them to be of modest potency (19). Their effectiveness also seemed to diminish with continuing treatment of recipients, a phenomenon attributed to the development of immunity to the heterologous protein. My interest was aroused as I wondered whether even a short course of such treatment, if the antiserum in question were sufficiently potent, might induce circumstances in which a substantial dose of dissociated cells of donor origin could produce a tolerance-like state in a recipient. With Tony Monaco, who had then joined us as a staff member after completing his training in surgery, we commenced testing antisera made in rabbits against lymphoid cells from mice. As high titers of antibody were desired we employed Freund's complete adjuvant with the immunizing cells from the beginning. This is not the place to recount all of the results of the many experiments that followed. The main initial point was that the sera we prepared proved to be remarkably powerful immunosuppressive agents which retained potency even over a long period of treatment (20,21). They produced greatly extended survival times for both allografts and xenografts.

Not long after this Peter Medawar became aware of our results and asked me for up-to-date information on our findings. He felt further investigation of such sera, and especially of their mechanism of action, might be a good subject for Raphael Levey to explore, as he was to go from our surgical residency program to join Peter for a year of fellowship experience at the National Institute for Medical Research at Mill Hill where Medawar had become director. The experiments which rapidly came forth from Medawar's laboratory on this subject were as interesting and valuable as one might have expected. The activity in this new field soon led to another fine Ciba conference on "antilymphocytic sera" in London (22). Here Tom Starzl presented his results with antisera to human cells which he had begun to test in kidney transplant recipient patients in Denver, and results from a number of other laboratories were summarized. We had found that the impact of antilymphocyte serum treatment, and their duration of action, were greatly potentiated by thymectomy even in adult individuals, and we had at last gotten around to exploring the capacity of serum treatment to create a tolerance responsive state in adult mice. This it could do quite strikingly if a sufficient number of donor strain cells was delivered intravenously. The process was also greatly abetted by adult thymectomy (23,24).

The development of antilymphocyte sera for use in clinical immunosuppression became a major goal for our research program. We first prepared batches of sera in rabbits against human lymph node or thymus cells by much the same recipe as we had employed for experiments in mice. As we had demonstrated that virtually all of the immunosuppressive potency of such sera resided in their gamma globulin fractions we elected to test column-prepared IgG fractions. The first studies were in a few human volunteers in which the effect of a brief course of treatment with a rabbit antihuman thymocyte serum on cutaneous delayed hypersensitivity responses and skin allograft survival were the end points. We recognized that the dosages we could deliver, considering the local inflammatory response elicited by serum injections, was very small compared to that which we knew to be so effective in the mouse. Accordingly we decided to make larger batches of sera and to use horses, younger ones if possible, as our antiserum factories. Ben Cosimi, while a research fellow in the laboratory, worked out the optimal plan for immunizing horses with human cells testing the sera prepared on primate subjects as surrogate patients. We constructed monstrous columns to separate out the IgG (25).

We began to test this material in patients and ultimately proved its considerable efficacy when given intravenously in larger doses to kidney transplant recipients who were undergoing acute rejection reactions (26). The testing of these antibodies by determining their capacity to reverse acute rejection reactions proved to be a key step for us as we could gather good initial evidence regarding their efficacy very promptly using a relatively small number of patients who could serve as their own controls.

Subsequently, we discussed the possibility of preparing even larger batches of such sera with representatives of the Upjohn Company. They expressed considerable interest and eventually set up the entire machinery to produce immunosuppressive sera at their headquarters in Kalamazoo, Michigan. Only with the expertise and resources of a company of this kind could such an agent find its way to more general use after approval by the Food and Drug Administration. All this occurred at a time when little thought was given to the commercial value of developments in our academic laboratories. We never gave any thought to patenting our process for making serum and, of course, never got into the complexities of financial benefits or conflicts of interest in connection with the effort, a fact which I do not regret.

I will not try to cover even our own activities in the field of immunosuppressive sera completely, and there have, of course, been many other contributors to it. When the discovery of techniques for the production of monoclonal antibodies was developed we were naturally attuned to their potential use as immunomodulators. New surface epitopes on T lymphocytes and their functional implications were rapidly being characterized, and it was clearly desirable to improve upon our complex and variable polyspecific antibody preparations if possible. The advantages of monoclonal antibodies were expected to include the possibility of administering much smaller doses of protein to achieve the same therapeutic effect, the standardization of the biologic reagent used, and the potential of selecting particular cell surface antigens, and accordingly particular functional classes of cells, for attention. A number of antibodies with attractive properties had already been produced, and we selected one available from the Ortho Pharmaceutical Company for our first trial. There were several difficulties for me in this particular selection at the time. We had expected to employ in patients only antibodies which we had previously tested in Ben Cosimi's Cynomolgus monkey transplant system as many antibodies prepared against human T lymphocytes will also react with the T cells of this species. Unfortunately, that is not the case for the pan-T-cell reactive antibody which had been made by Patrick Kung, then at Ortho. Furthermore, this antibody was known to have strongly mitogenic effects on human T cells in vitro, and it was thought that it might actually potentiate rather than inhibit transplant rejection. We made the decision to proceed with its trial in patients in spite of the uncertainties involved and were all greatly relieved when our first patient showed total disappearance of T lymphocytes from his peripheral blood in five minutes after receiving only 2 mg of OKT3 intravenously. This occurred in association with only a mild febrile reaction in this patient, although early reactions of varying magnitude to the antibody have required special precautions for its safe and successful use (27). Since then this monoclonal has been subjected to extensive evaluation, especially as an agent for reversing early acute transplant rejection

with Jon van Rood, visiting ca. 1966.

with Henry Winn

with R.E. Billingham and M.F.A. Woodruff, 1974.

with A strain mouse bearing skin and kidney transplants.

reactions (28). The Ortho people (especially Gideon Goldstein) secured acceptance of their antibody by the FDA and brought it rapidly to market. Again, I should mention, there were no financial considerations for any of our group personally. OKT3 has been of interest in a number of ways but perhaps particularly as it still may point the way toward even more effective agents in the same class, agents which will be part of better approaches to our original objective, a treatment program designed to promote long-term immunological unresponsiveness to the antigens of a given donor.

In the nearly 30 years during which our laboratory has been functioning uninterruptedly we have naturally followed many lines of investigation. I have enjoyed participating in a number of them to one degree or another, although many have been carried out independently by capable colleagues, often with the participation of research fellows whom we have been fortunate enough to draw from many parts of the world. Of those in which I have been engaged I will mention only a few here in order to suggest the range of our interests.

The work mentioned above, in which Henry Winn defined the effects of appropriate antisera on transplanted tissues in vivo, occupied considerable attention in the early 1970s. Antibody treatment could cause the destruction within hours of previously beautiful and supple skin grafts which were surviving by virtue of appropriate immunosuppression. We found that this reaction depended upon the grafts being reperfused through their own vessels where surviving donor-specific endothelium was the first object of attack. After several weeks this endothelium was replaced by cells of recipient origin making the grafts impervious to destruction by antibody. We also found that the acute reaction depended upon the participation of serum complement and polymorphonuclear leukocytes (5).

Another set of experiments, of particular interest to me, can be conveniently mentioned together as they all employed the transplantation of organs, mostly in the mouse, by microsurgical techniques. A clever and persistent research fellow from Poland, Marek Skoskiewicz, along with my senior technical associate for many years, Catharine Chase, were able to devise a successful procedure for the transplantation of the kidney in the mouse (29,30). Later Robert Corry built on this experience to contrive a technique for transplanting the mouse heart heterotopically into the abdomen with appropriate vascular anastomoses (31). The insight into immune responses which one can gain through the use of subjects which are highly characterized genetically has been emphasized above. When one sets out to compare such responses to different tissues a well understood genetic background is of special value. We have learned a lot with these systems, much more than I should try to relate here.

One of the most intriguing series of observations was made with the mouse kidney transplantation system. We found that kidney transplants between mice which were incompatible in respect to antigens determined at the major histocompatibility complex, even several strain combinations which differed by multiple H-2 and non-H-2-determined specificities, would go through a period of active rejection, usually with some elevation of their blood urea nitrogen levels, before rejection would subside spontaneously and permanently with clearance of the typical cellular infiltrate visible in sections of removed kidneys. Since both of the recipients' kidneys had been removed at the time of transplantation we could follow the functional state of the transplant closely. After rejection had settled down it left the bearers of these transplanted kidneys in a state of greatly reduced responsiveness to the foreign antigens present in the transplanted kidneys as could be shown by the fact that they would generally accept donor strain skin grafts for many months. A

Transplantation Unit Laboratory, 1970

Front Row: D. Accetta, F. Chavez-Peón, I. MacKenzie, H. Winn, P. Russell, D. Sachs, G. Monchik;
Middle Row: C. Chase, F. Gerardi, M. Bianco, E. Skamene, L. Davies;
Back Row: J. Cavallaro, K. Stenger, R. Laufer, D. DiPadua, A. Skamene, H. O'Connor, C. Baldamus.

Panel Discussion - Transplantation Society, 1966

(Left to right) P.B. Medawar, B. Benacerraf, H. Balner, F. Rapaport, H.S. Lawrence, J. Dausset, P.S. Russell.

strikingly different result was achieved when slices of kidney tissue from the same donor strains were simply implanted into the leg muscles of recipients according to the technique we had often used previously for endocrine transplantation. Here, exposure to donor antigens left recipients highly immunized to these same antigens so that skin grafts were dispatched in typical accelerated fashion. We have made some efforts to explore the mechanism of this intriguing tolerance-like phenomenon, which we believe to be an important one, perhaps often seen in our patients to some degree. As yet no definitive conclusions have been reached, but we have not given up the effort as there are now much better methods with which to pursue it.

Other things which have attracted our attention in more recent years include the heightened expression of histocompatibility antigens during rejection (32) and the dependence of this process on the release of lymphokines, especially gamma interferon (33). We have pursued a few experiments on the transplantation of islets of Langerhans in the mouse, some experiments on intestinal transplantation in rats, with particular attention to the development of graft-versus-host reactions mounted by the transplanted bowel (34), and more recently some studies on the mechanism whereby proliferative endovascular lesions appear in transplanted organs and some approaches to their prevention.

I have shared the feeling of many others that replacement of normal islet cell function by some form of transplantation should be of major benefit to diabetic patients in due course. We now have some useful experience with transplantation of the whole pancreas in diabetic patients, enough for me to conclude that replacing islet function is an objective worth reaching, but in the long run it must be done in a far safer and simpler fashion. Islet transplantation continues to look gradually more promising as the next step, but even if successful allogeneic islet transplantation can be accomplished, and even if this could be done without immunosuppression, we would be left with important problems well known to those close to the subject. These would include the difficulties of securing sufficient donor tissue and the issue of continuing reactivity against the donor islets as a consequence of ongoing autoimmune reactivity aimed in their direction. Xenospecific sources may offer a feasible way around the first, and perhaps even the second of these obstacles, and active interest in the biology of xenospecific immune responses has been growing rapidly in recent years. In our group we have paid attention to aspects of this area for some time but only recently has a concentrated effort been undertaken by Hugh Auchincloss to contribute systematically.

Another possible alternative has also caught our attention, and Marek Skoskiewicz and I have done a few experiments with this line of investigation in collaboration with the head of our large laboratory of molecular biology, Howard Goodman, and one of his younger colleagues, Richard Selden. The approach is to empower cells other than islet cells to produce insulin by transferring functional copies of the gene sponsoring insulin production into them. The transfer is done by transfecting cells in culture. We have been able to accomplish this successfully in that the human insulin gene has been transferred into cultured mouse fibroblasts which will then make human insulin in large quantities. When transplanted into diabetic mice such transfected cells will depress the blood sugar to normal levels, but their recipients then go on to develop hypoglycemia and eventually die as insulin production is not normally regulated in these cells (35). There is much that can be done along these lines, and it seems to me that such work may be quite revealing of the fundamental biology of diabetes as well as offering some possibilities for useful application.

I mention these latter experiments in order to suggest we should be alert to the likelihood that the boundaries of transplantation medicine and surgery can be extended broadly as the knowledge now becoming available will surely equip those entering the field to make advances into altogether new realms unthinkable in the early days of the subject, recent as they were.

Final Commentary

As clinical transplantation has grown it has come under greater scrutiny because of its cost, because of uncertainty regarding the equity with which its life saving benefits are meted out, and because transplantation of some organs has been tagged with the crippling epithet, "experimental" in certain quarters. At the same time new organizations have sprung up in efforts to coordinate the delivery of transplantation operations to patients and to regulate the collection and distribution of organs. Intense consideration of ethical questions by many in the field, and not a few outside of it, has resulted. Much can be said about this relatively recent aspect of transplantation as it has become a large subject. Its development has resulted, of course, from the increasing success of organ transplantation. When one surveys the wide range of activity which can impinge closely upon the welfare of transplant recipients it proves to be a fascinating array stretching all the way from molecular biological considerations through numerous physiological and pathological mechanisms to the complexities of individual patient care and hospital management finally to include fundamental societal questions.

I believe that virtually all aspects of the field are closely linked to scientific progress and are accordingly technology driven. The costs of a given transplant, the patients who are appropriate to receive it, the advisability of sharing organs widely, and many other practices can be expected to change with scientific progress. One cannot, by the very nature of the scientific process, foresee what will become known in the future where knowledge is now lacking. Still there *is* enough known already on which to base a strong sense of confidence that certain types of technological improvements will continue. Surely we can expect that greatly improved methods for the preservation of organs for transplantation will be found. At least some valuable uses will be found for living animal tissues as replacements for their human counterparts, uses which may even include whole functioning organs. The place that knowledge of transplantation biology will play in the delivery of new genetic information to appropriate patients is, of course, not yet clear, but those in the field should be alert to opportunities which will emerge in this area. All concerned must accordingly be prepared to adapt to the changes which will come, changes which can be expected to have major and continuing effects. As I look back over what has occurred in the past 38 years, it would be folly to predict otherwise.

Festschrift for Paul S. Russell, November 1990.

REFERENCES

1. Billingham RE, Russell PS. Studies on wound healing with special reference to the phenomenon of contracture in experimental wounds in rabbits' skin. Ann Surg 1956; 144:961.

2. Medawar PB, Russell PS. Adrenal homografts in mice with special reference to "immunological adrenalectomy". Immunology 1958; 1:1.

3. Gorer PA. Role of antibodies in immunity to transplanted leukemia in mice. J Pathol Bacteriol 1942; 54:51.

4. Billingham RE, Brent L. Further attempts to transfer transplantation immunity by means of serum. Br J Exp Pathol 1956; 37:566.

5. Winn HJ, Baldamus CA, Jooste SV, Russell PS. Acute destruction by humoral antibody of rat skin grafted to mice: the role of complement and polymorphonuclear leukocytes. J Exp Med 1973; 137:893.

6. Russell PS, Gittes RF. Parathyroid transplants in rats: a comparison of their survival time with that of skin grafts. J Exp Med 1959; 109:571.

7. Gittes RF, Russell PS. Male histocompatibility antigens in mouse endocrine tissues. J Natl Cancer Inst 1961; 26:283.

8. McGovern JJ, Russell PS, Atkins L, Webster EW. Treatment of terminal leukemic relapse by total body irradiation and intravenous infusion of stored autologous bone marrow obtained during remission. N Engl J Med 1959; 260:675.

9. Russell PS, Wood ML, Gittes RF. Preservation of living tissue in the frozen state. J Surg Res 1961; 1:23.

10. Simmons RL, Russell PS. The antigenicity of mouse trophoblast. Ann NY Acad Sci 1962; 99:717.

11. Healey WV, Russell PS, Poole HK, Olsen MW. A skin grafting analysis of fowl parthenogens: evidence of a new type of genetic histocompatibility. Ann NY Acad Sci 1962; 99:698.

12. Russell PS. Modification of runt disease in mice by various means. In: Wolstenholme GEW, Cameron MP, Eds. Ciba Foundation Symposium on Transplantation. Churchill, London, 1962; 350.

13. Gowans JL. The fate of parental strain small lymphocytes in F1 hybrid rats. Ann NY Acad Sci 1962; 99:432.

14. Schwartz R, Dameshek W. Drug-induced immunological tolerance. Nature (London) 1959; 183:168.

15. Krohn PL. Effect of ACTH and cortisone on survival of skin homografts and on adrenal glands in monkeys (Macaca mulatta). J Endocrinol 1955; 12:220.

16. Jeannet M, Pinn V, Flax MH, Winn HJ, Russell PS. Humoral antibodies in renal allotransplantation in man. N Engl J Med 1970; 282:111.

17. Russell PS, Winn JH, Amos DB, Eds. Histocompatibility Testing. National Academy of Sciences/National Research Council, Washington, DC, 1965.

18. Woodruff MFA, Anderson NF. Effect of lymphocyte depletion by thoracic duct drainage and administration of antilymphocytic serum on survival of skin homografts in rats. Nature (London) 1963; 200:702.

19. Sacks JH, Filippone DR, Hume DR. Studies of immune destruction of lymphoid tissue. I. Lymphocytotoxic effect of rabbit anti-rat lymphocyte antiserum. Transplantation 1964; 2:60.

20. Gray JG, Monaco AP, Wood ML, Russell PS. Studies on heterologous anti-lymphocyte serum in mice. I. In vitro and in vivo properties. J Immunol 1966; 96:217.

21. Monaco AP, Wood ML, Gray JG, Russell PS. Studies on heterologous anti-lym-

phocyte serum in mice. II. Effect on the immune response. J. Immunol. 1966; 96:229.

22. Wolstenholme GEW, O'Connor M, Eds. Ciba Foundation Study Group No. 29 Antilymphocytic Serum. Churchill, London, 1967.

23. Monaco AP, Wood ML, Russell PS. Studies on heterologous anti-lymphocyte serum in mice III. Immunological tolerance and chimerism produced across the H-2 locus with adult thymectomy and antilymphocyte serum. Ann NY Acad Sci 1966; 129:190.

24. Russell PS, Monaco AP. Heterologous antilymphocyte sera and some of their effects. Transplantation 1967; 5:1086.

25. Cosimi AB, Skamene E, Bonney WW, Russell PS. Experience with large-dose intravenous use of antithymocyte globulin in primates and man. Surgery 1970; 68:54.

26. Cosimi AB, Wortis HH, Delmonico FL, Russell PS. Randomized clinical trial of antithymocyte globulin in cadaver renal allograft recipients: importance of T cell monitoring. Surgery 1976; 80:155.

27. Cosimi AB, Colvin RB, Burton RC, Rubin RH, Goldstein G, Kung PC, Hansen PW, Russel PS. Use of monoclonal antibodies to T-cell subsets for immunological monitoring and treatment in recipients of renal allografts. N Engl J Med 1981; 305:308.

28. Ortho Multicenter Transplant Study Group. A randomized clinical trial of OKT3 monoclonal antibody for acute rejection of cadaveric renal transplants. N Engl J Med 1985; 313:337.

29. Skoskiewicz MJ, Chase CM, Winn HJ, Russell PS. Kidney transplants between mice of graded immunogenetic diversity. Transplant Proc 1973; 5:721.

30. Russell PS, Chase CM, Colvin RB, Plate JMD. Kidney transplants in mice: an analysis of the immune status of mice bearing long-term H-2 incompatible transplants. J Exp Med 1978; 147:1449.

31. Corry RJ, Winn HJ, Russell PS. Primarily vascularized allografts of hearts in mice. The role of H-2D, H-2K, and non-H-2 antigens in rejection. Transplantation 1973; 16:343.

32. Benson EM, Colvin RB, Russell PS. Induction of IA antigens in murine renal transplants. J Immunol 1985; 134:7.

33. Skoskiewicz MJ, Colvin RB, Schneeberger EE, Russell PS. Widespread and selective induction of major histocompatibility complex-determined antigens in vivo by gamma interferon. J Exp Med 1985; 162:1645.

34. Monchik GJ, Russell PS. Transplantation of small bowel in the rat: technical and immunological considerations. Surgery 1971; 70:693.

35. Selden RF, Skoskiewicz MJ, Russell PS, Goodman HM. Regulation of insulin gene expression. Implications for gene therapy. N Engl J Med 1987; 317:1067.

CURRICULUM VITAE

Paul S. Russell

PERSONAL

Born: January 22, 1925; Chicago, Illinois
Marital Status: Allene Lummis, 1952; 4 children

EDUCATION

1944	University of Chicago, PhB.
1945	University of Chicago, B.S.
1947	University of Chicago, M.D.
1962	Harvard University, M.A. (Honorary)

POSITIONS

1948-56	Surgical Intern and Resident, Massachusetts General Hospital, MGH
1954-55	Research Fellowship, Department of Zoology, University College, London (Professor P.B. Medawar)
1957-60	Instructor and Clinical Associate in Surgery, Harvard Medical School, HMS
1957-60	Assistant in Surgery, MGH
1960-62	Associate Attending Surgeon, Presbyterian Hospital
1962-69	Chief, Surgical Services, MGH
1962-	John Homans Professor of Surgery, HMS
1969-	Visiting Surgeon, MGH
1969-90	Chief, Transplantation Unit, MGH

MILITARY SERVICE

1951-53	United States Air Force

PROFESSIONAL SOCIETIES

New York Academy of Sciences
American College of Surgeons
Society of University Surgeons
Society of Experimental Biology and Medicine
American Association for Thoracic Surgery
New England Surgical Society
American Surgical Association
The Transplantation Society
    1970-72 President
American Society of Transplant Surgeons
Royal Society of Medicine
Hellenic Surgical Society
Polish Academy of Sciences

EDITORIAL BOARDS AND EDITORSHIPS

Surgery
Archives of Surgery
Monographs in the Surgical Sciences
Transplantation
The Journal of Immunology
Annals of Surgery
Transplantation Proceedings

COUNCIL AND ADVISORY COMMITTEE MEMBERSHIPS

1962-70	Subcommittee of Professors, HMS
1962-	Executive Committee on Research, 1973-79 Chairman, MGH
1963-69	General Executive Committee, 1965-67 Chairman, MGH
1963-79	Dunham Lecture Committee, 1974-79 Chairman, HMS
1963-67	Allergy and Immunology Study Section, NIH, 1965-67 Chairman
1963-68	Committee on Trauma, NAS/NRC
1963-71	Committee on Tissue Transplantation, NAS/NRC
1967-	Committee on Teaching and Education, MGH
1967-72	Transplantation and Immunology Committee, NIAID, 1970-72 Chairman
1969-90	Trustee, New England Organ Bank, 1969 Founding Chairman
1971-73	Committee to Study Clinical Investigation and Education in the Navy, NAS/NRC
1974-79	Committee on Cancer Immunotherapy, National Cancer Institute
1978-79	Consultant, National Center for Health Care Technology
1978-82	Committee on Promotions and Reappointments, HMS
1978-84	Secretary, Faculty of Medicine, HMS
1981-	Chairman, Committee on Research Planning and Policy, MGH
1981-83	Advisory Committee to Harvard Corporation on Shareholder Responsibility, HMS
1982-	Committee on Faculty Conduct 1988- Chairman, HMS
1982-91	Committee on Space, MGH
1983	Planning Group, Concensus Conference on Liver Transplantation
1983-84	Task Force on Organ Transplantation, Department of Public Health, Massachusetts
1984-88	NHLBI Research Review Committee A
1985-86	Task Force on Organ Transplantation of the Health Resources and Services Administration, Department of Health and Human Services

1985-	Statewide Health Coordinating Council, Massachusetts
1985-	Chairman, Policy Board, National Liver Transplantation Database, NIADDK
1989-	Chairman, Joint Committee on The Countway Library of Medicine, HMS

INDUSTRIAL CONSULTANTSHIPS

1969-74	American Optical Company
1974-	Warner-Lambert Company, Board of Directors
1986-	Neomorphics, Inc.
1988-	Witikar Saudi Arabia Limited

EDUCATIONAL AND PHILANTHROPIC

1964-79	Board of Trustees, Groton School
1963-76	Board of Trustees, Pine Manor College
1968-	Board of Directors, Boston Fulbright Committee, 1980- Chairman

PUBLICATIONS

Total: 240

FROM THE EARLY DAYS OF HUMAN KIDNEY ALLOTRANSPLANTATION TO PROSPECTIVE XENOTRANSPLANTATION

G.P.J. Alexandre

Address: Department of Renal and
Pancreatic Transplantation
Cliniques Universitaires Saint Luc
10 Avenue Hippocrate
1200, Brussels, Belgium
02-764-2206

G.P.J. Alexandre

FROM THE EARLY DAYS OF HUMAN KIDNEY ALLOTRANSPLANTATION TO PROSPECTIVE XENOTRANSPLANTATION

G.P.J. Alexandre

Introduction

Immediately upon receiving my medical degree from the University of Louvain Medical School in Louvain, Belgium, it was clear to me that I wanted to become a surgeon. I applied to Professor J. Morelle, Chief of the Department of Surgery at the Cliniques Universitaires Saint Pierre in Louvain, where I was accepted as an assistant.

Professor Morelle was a general surgeon, but he had a special interest and competence in the neurosurgical sciences, which revealed itself as a determining factor in the beginning of the transplantation era at our center.

In his department, it was customary to spend a year abroad during the third year of surgical training. For the most part, the decision as to where to go depended on individual wishes. In my case, this decision turned out to be the decisive factor which influenced my surgical career. It was a consequence of a review I had done on "immunology and transplantation" which focused my interest on the field of transplantation.

I obtained a C.R.B. graduate fellowship for a year of surgical research to be spent in the laboratory for surgical research at the Harvard Medical School in Boston, under the direction of Professor Joseph Murray and in the Department of Surgery of the Peter Bent Brigham Hospital, directed by Professor Francis D. Moore.

The Good Years

It is difficult to describe the state of mind of a young graduate in medicine, arriving in the States with his wife and two babies in September 1961, while speaking imperfect English and having even more imperfect understanding. Fortunately, the friendly people we were extremely lucky to meet on our arrival in Boston, helpfully guided our first steps toward establishing ourselves.

My initial contact with Dr. Murray's laboratory was Dr. Roy Calne. He was packing to return to England and gave me advice on how to treat the dogs that were surviving from his experiments with a functional kidney transplant.

Considerately, Dr. Murray gave me a few weeks to "accommodate" before beginning the real work. At that time, the main goal of research was to find new immunosuppressive drugs and regimens. Regular discussions on how to improve the immunosuppressive effects of BW-57322, the actual name of Imuran, were conducted at Burroughs Wellcome headquarters with Drs. G. Hitchings and Trudy Elion (who also received the Nobel prize since then).

During my stay in Dr. Murray's laboratory, hundreds of dogs received a kidney allograft in an effort to find the best immunosuppressive regimens. These were times when up to five kidney transplants a day were being performed in the laboratory with a team consisting of two technicians and me; still, weather permitting, I was often spared some time to play tennis at midday with my Peruvian technician. It was great! Everybody was enthusiastic and excited about the results.

One drug combination, azaserine and actinomycin D, gave especially good results, which were reported to the Congress of the AMA at Atlantic City since the entire series of 16 dogs had retained a functioning kidney for more than 20 days, a record in those days.

This drug combination was considered good enough to be used in clinical practice. I was then given the responsibility of preparing the azaserine solution to be administered to the transplanted patients at the Brigham Hospital. With this priceless solution in hand, I could enter the patient's rooms in the evening, often with suspicious looks from the nurses because of what I was doing to their patients. Needless to say, everything had to be explained in great detail! Looking back at this period of my life, I must confess that it was probably the most enjoyable and the most exciting. It became clear that long-lasting functioning renal allografts could be obtained in dogs with nonspecific immunosuppressive regimens. And if it were possible in dogs, it surely would also be the case in man. I returned to Belgium with this good news to complete my surgical training.

The First Kidney Transplant in Belgium

With some azaserine and actinomycin D in my luggage, the return trip was made in the hope that kidney transplantation could also be started in Belgium. Convincing everybody of the feasibility of the procedure was not an easy task but, fortunately, my department chief supported the idea. He was even more convinced after we had repeated the surgical procedure twice on a cadaver.

All that remained was to find a suitable patient and to maintain him in a suitable condition until a kidney could be obtained and transplanted. Since no chronic dialysis apparatus was available in our department at that time, the first patients were maintained with peritoneal dialysis, performed by medical students on a voluntary basis and in 24-hour rotation.

On June 3, 1963, a patient was brought in with a head injury and in profound coma. The patient became completely areactive, had a falling blood pressure despite the administration of vasopressive drugs, and presented all the signs of what Mollaret had described as a "coma dépassé," a notion which has since been anatomically confirmed by Inkvaard.

Professor Morelle, who was quite experienced in neurosurgery, considered the neurological symptoms presented by the patient and took what today could be considered the most important decision of his career: whether to remove a kidney from that patient while the heart was still beating. This procedure was probably the first transplant ever removed from a heart-beating cadaver. Fortunately, this was long before the days of established ethical committees.

The kidney was transplanted without delay. In fact, the kidney was removed by Professor Morelle and his team while another team and I were preparing the recipient in an adjacent room. No preservation fluid was used; the blood contained in the transplant was not even washed away; the graft functioned right away without tubular necrosis; and the patient's serum creatinine was back to normal within a few days. Unfortunately, this patient died from sepsis of the wound after three months. His follow-up, however, took long enough to convince other colleagues that the procedure could be done and that drug immunosuppression was effective.

At the time of this first patient's death, three other patients had been transplanted. The third patient was transplanted with a living donor kidney given by the patient's uncle. That patient's kidney functioned for more than six years as did the kidney of the fourth patient transplanted with a cadaver kidney.

With these two long-term survivors, the transplant program at our center was launched. From then on, the number of transplants performed annually has increased progressively and the program has been adapted to the latest progress.

The Birth of Eurotransplant

In 1967, Dr. Jon van Rood presented the idea of selecting the recipient of a cadaver kidney in accordance with the compatibility of the donor and recipient leukocyte antigens. Only a small number of HLA antigens could be determined at that time. Those were the days of the antigens 4a, 4b, 6a, 6b enz. The difficulty, however, was the kidney preservation since the preservation solutions were far less effective; therefore, there was a real need for expediting all the procedures at maximum speed.

Fortunately, Dr. van Rood's laboratory in Leiden, Holland, is not so far from Belgium, and I must confess we received maximum logistical support from the Belgian police corps and the light aviation unit of the Belgian Army. When a donor was available, blood was sent by helicopter or car to Leiden, and as soon as the results of the HLA antigens were known, the kidneys were delivered to the best available match. In the beginning, these exchanges were restricted between Holland and Belgium. For some years, one army helicopter was reserved strictly for these missions and was known in the army as the "kidney helicopter".

When the distance was not too great or a donor kidney became available at night, one of us did the transporting. Dr. P. J. Kestens, well known among us for his fast driving (presently Professor of Surgery and Chief of the Department of Surgery at our Clinics), once had an auto accident while transporting a kidney at a time when the recipient was already prepared in the operating room. The only way the kidney could arrive safely and in time was for Dr. J. J. Rombouts, who had accompanied Dr. Kestens, to hitch-hike. Fortunately, it did not take too long.

Antilymphocyte Serum "House Made"

After Dr. Thomas Starzl showed that better renal transplantation results could be obtained by treating recipients with antilymphocyte serum, we embarked on the local preparation of horse antihuman antilymphocyte serum. Horses disqualified for duty because of lameness were bought from our National Mounted Police Corps and injected with thoracic duct lymphocytes. These were being collected from recipients of living donor kidneys who, in that period of time, were prepared at our center with a five-day preoperative drainage of the thoracic duct.

The horses were housed at a local farm, and we had the responsibility of injecting the antigenic material ourselves. Fortunately, the farmer was well aware of all the tricks of keeping the horses quiet during the injections! Still, we were a bit afraid that they could react violently and kick us out of the stall. After immunization, the horses were brought to the laboratory where a horse box had been built, and there they were bled. Professor G. Sokal, head of the immunohematology laboratory took the responsibility of extracting the antilymphocyte globulins and prepared the vials for injection to the patients. Since the preparation of this ALG was cumbersome and somehow monopolized the laboratory activities, contact was made with Behringwerke Pharmaceuticals (Germany) which took over this preparation which led to the commercialization of the Behring horse antihuman ALG, a very active, well-known product around the world today that has been administered to thousands of transplanted patients. A prospective randomized series at our center clearly demonstrated the benefit of ALG in human renal transplantation, and since October 1976, it has been used prophylactically in all patients at our center.

Dr. J. P. Squifflet joined our staff in 1978. In 1981, he obtained a research fellowship grant at the University of Minnesota in Dr. J. Najarian's department, where he began a PhD program in pancreatic transplantation under Dr. D. Sutherland's supervision. A few months after Dr. Squifflet returned from Minneapolis, the first pancreatic transplant was performed in our department, actually the first ever done in Belgium, and the beginning of our pancreatic transplant experience.

ABO-Incompatible Transplants

Early in 1981, we accidentally performed an ABO-incompatible cadaver kidney transplant which turned out to be a blood group A1 into an O recipient. At the time the error was discovered, the patient had already been transplanted. Since the graft function was excellent, the patient was heparinized but otherwise received the standard triple immunosuppressive therapy consisting of prophylactic antilymphocyte serum (ALG, Behringwerke, Germany), Imuran, and low-dose steroids.

The follow-up was uneventful until the beginning of the third week, at which time a rejection crisis developed with a sharp increase of the anti-A isoagglutinins which reached a titer of 1/20,000. Antirejection therapy consisted of boluses of methylprednisolone and antilymphocyte serum. Complete control of the rejection crisis was obtained without much difficulty; the isoagglutinin titer decreased and the renal function has remained normal since. The patient is now more than nine years posttransplantation.

The happy ending to this particular case led us toward a renewed interest in the possibility of achieving ABO-incompatible transplants. By discussing the matter with Drs. M. De Bruyère and D. Latinne, respectively Professor of Medicine and Associate Chief of Laboratory in the Immunohematology Department and with Dr. M. Moriau, Professor of Medicine in the Hematology Department at our University clinics, we thought we could use a similar approach to that used in achieving ABO-incompatible bone marrow transplants to prepare recipients for ABO-incompatible living-donor kidney transplants.

The first application of this clinical protocol was the case of a 9-year-old girl with blood group O who was prepared to receive her mother's A1 kidney by preoperative plasmaphereses to get rid of the antidonor isoagglutinins. After the last plasmapheresis, we administered soluble substance A to eliminate the remaining isoagglutinins. The recipient was splenectomized at the time of and immediately prior to grafting. At that time, splenectomy of the recipient was routinely performed in all cases of living-donor kidney transplantation at our center. This was also the case for living-donor ABO-compatible kidney transplantation. Fortunately, the postoperative follow-up of this case was uneventful. Renal function became normal after a few days and has remained so. No rejection was ever noticed. Encouraged by this case, we decided to go on. At that time, the recipients of living-donor ABO-compatible kidney transplants at our center were being prepared preoperatively with donor-specific blood transfusions (DST). We thought that the recipients of an ABO-incompatible kidney should also benefit from DST but, for obvious reasons, whole blood could not be used. Therefore, it was decided to use donor-specific platelet transfusions (DSPT) instead, since platelets do not contain ABO blood group antigens. The experience with DSPT in ABO-incompatible transplants demonstrated the same disadvantage as using DST in AB0-compatible transplants, ie, the production of sensitization to the donor-specific blood products that prevent the living-donor transplant in ±10% of the cases. Therefore, the use of DSPT was halted.

Since the first five ABO-incompatible cases succeeded without much difficulty, we were confused by the failure of the following three consecutive cases which we attributed to the fact that these three patients were not splenectomized. The reason splenectomy was omitted resulted from a change in our protocol in living-donor kidney transplantation. As explained previously, at the time ABO-incompatible living-donor transplantation was initiated at our center, splenectomy of the recipient was part of the standard protocol being used in this category of patients. Therefore, the decision to abandon splenectomy in living-donor kidney transplantation was taken, irrespective of the ABO-compatibility or -incompatibility of the donor.

After the third consecutive failure, we realized that the only change we had made in our protocol relative to the first five cases was indeed the splenectomy, which we had omitted in the last three cases. Although no clear-cut scientific conclusion could be drawn from such a small series, it was decided to reintroduce prophylactic splenectomy in the protocol of ABO-incompatible living-donor kidney transplantation as a standard measure. A more scientific approach would have been to start a randomized prospective study of splenectomy against no splenectomy in this category of patients but due to the three consecutive failures which we experienced, it was felt that such a study was ethically unacceptable.

The observation that isoagglutinins could be allowed to return after transplantation without necessarily producing an irreversible rejection of the transplant surprised us. More disturbing, but even more interesting, is the fact that some patients may carry very high titers of isoagglutinins, much higher than prior to the transplant and still tolerate the ABO-incompatible kidney quite normally, as if the transplant had become indifferent to these antibodies.

Meanwhile, we could demonstrate that the ABO blood group antigens have not disappeared from the endothelium of the transplanted kidney. Indeed, if one takes a biopsy of a well-tolerated ABO-incompatible kidney and challenges this kidney tissue with the patient's own serum in vitro, there is a clear-cut fixation of the patient's isoagglutinins on the endothelium, clearly demonstrating that the antigens are still in place. Why these antibodies which react in vitro do not react in vivo is unknown. Dr. F. Bach proposes the word "accommodation" to name this phenomenon whereby the three major components of an immunological reaction, ie, a mixture of antigens, complement, and specific antibodies do not react together.

J. Platt proposes several explanations for this phenomenon of accommodation:

- a change in the susceptibility of the graft endothelial cells to injury from the isoagglutinins
- a change in affinity and/or specificity from the natural antibodies present before grafting
- a modulation of the epitopes normally expressed by the graft endothelial cells.

From our clinical experience, it appears that a rapid postoperative increase of the antibody titer generally leads to irreversible graft rejection while those patients maintaining a low profile of these antibodies generally enjoy normal functioning transplants.

Therefore, a primary condition to obtain accommodation must be the control of the postoperative production of the natural antibodies during the initial postoperative period. In our ABO-incompatible series of patients, we never observed any humoral crisis of rejection after the third postoperative week, which indicates that probably a critical period exists during which the ABO-incompatible transplant is at risk of acute vascular (humoral) rejection, but after which, the transplant behaves in a conventional manner.

Another observation is that in a particular patient, we never observed two successive vascular rejections so that the accommodation may be either produced progressively when the patient does not present any rejection crisis, or the accommodation installs itself at the outset of a well-controlled rejection crisis. Since the majority of patients receiving an ABO-incompatible kidney transplant present one rejection crisis, one may believe that accommodation is brought about in the majority of cases when the patient is coming out of a successfully treated rejection crisis.

Whatever the mechanism of accommodation may be, it is important to realize that it allows successful transplantation across preformed antibodies which opens the barriers of xenotransplantation.

Pig-to-Baboon Renal Xenotranplantation

The major obstacle to xenografting between discordant animal species such as pig-to-baboon or pig-to-man is also represented by natural preformed antibodies (NPA) of the recipient species against the donor species producing acute vascular irreversible rejection of the transplanted organ. There is, therefore, a similarity between ABO-incompatible renal transplantation in the human and renal discordant xenotransplantation since NPA are responsible for the violent vascular rejection phenomenon observed in both models.

Similar to the situation existing in human ABO-incompatible renal transplantation, manipulation of these natural antibodies in such a manner as to avoid the triggering of the xenograft rejection phenomenon is a prerequisite for successful long-term organ xenografting.

Owing to the success obtained in our series of ABO-incompatible renal transplants, we chose to explore the possibility of achieving pig-to-baboon renal xenotransplantation. In doing this, we obtained the full support of W. De Meurichy, Dr. of Veterinarian Medicine at the Koninklijke Maatschappij voor Dierkunde of Antwerpen and Professor A. Dewaele, Chief of the Department of Pathology at the Faculty of Veterinarian Medicine of the University of Liège.

We thought that if "the same causes produce the same effects," then treating a baboon recipient of a pig kidney by the same regimen as a human recipient of an ABO-incompatible renal allograft could permit a breach to the barrier presented by the NPA in the field of xenotransplantation.

In October 1984, the first pig-to-baboon renal xenograft was thus performed in our laboratory for surgical research and to our great satisfaction, this renal xenograft succeeded in maintaining a satisfactory function for 13 days, whereas controls lasted a maximum of 35 minutes to a few hours. The combination of preoperative plasmapheresis with splenectomy and a quadruple immunosuppressive therapy demonstrated its effectiveness in prolonging a discordant renal xenograft far beyond the survival time that had been obtained so far in this type of model.

Although some eminent immunologist told us that this prolongation was nothing more than a "ball chance," we carried on with the help of Drs. P. Gianello and D. Latinne but chose to use rhesus monkeys instead of baboons. The change in animal species was suggested by financial and logistical considerations. This idea, however, did not turn out to be a very good one. The very small caliber of the vessels caused many difficulties in achieving plasmapheresis in these animals. Therefore, after a series of technical failures, we therefore switched back to our initial idea of using baboons.

To date, a dozen pig-to-baboon renal xenografts have been achieved. In this series, three animal recipients are worthy of more detailed description since they sur-

Operating team consisting of Drs. M. Carlier, J.P. Squifflet, and G.P.J. Alexandre watches the donor for the first pig-to-baboon renal xenograft performed in October 1984.

The first pig-to-baboon renal xenograft after revascularization has a normal appearance while it has already started functioning.

The first baboon recipient of a pig kidney awakes from anesthesia.

vived 10, 22, and 23 days, respectively. The baboon who lived for 10 days died of a pulmonary infection; the renal function was normal (1 mg%) at the time of death and histology of the xenograft at the time of death was remarkably normal. The two baboons who lived over three weeks presented a normal renal function during the first postoperative days. Each of them presented an acute rejection crisis at the end of the first week, but while this rejection crisis was vascular (humoral) in nature for the first animal, it was strictly cellular and mild in the second one.

This example of an interstitial cellular rejection in a discordant xenograft model is the first of its kind that we know of. It represents an indication that once the obstacle of the humoral barrier is overcome, the better known cellular rejection remains to be avoided, which, according to some reports, could be easier to handle in xenografts than in allografts.

Organ Transplantation in the Future

In a relatively short period of time (30 years) organ transplantation has become a very effective therapy to treat an extensive number of lethal diseases. Patients who were condemned to death only a few years ago return to active life with a well-functioning organ transplant. Double organ transplantation like heart and liver, heart and kidney, heart and lungs, kidney and pancreas, triple organ transplantation like heart, liver, and kidney or even more complex organ transplants like the cluster organ transplants, have become possible with good success.

There is, however, a shortage of organs which will increase even further with the broadening of the indications for organ transplantation and the need for retransplantation in cases of chronic rejection. The challenge for the coming years is clear: we must find a way out of the shortage of transplantable organs while at the same time unspecific and specific immunodepressive means need to be developed and refined.

In my opinion, xenotransplantation is the way to go. We have shown that the humoral barrier is not insuperable; new immunosuppressive drugs are being discovered, which alone, or most probably in combination, will allow for better control of the immunological reaction. Unspecific immunosuppression may be combined with more specific means to produce specific tolerance. These, together with an appropriate preparation of the donor animal and the recipient patient, should allow for acceptance of a xenografted organ in the not too distant future. Then we will have achieved our goal to transplant all the candidates for organ transplantation without being compelled to register the patients on evergrowing waiting lists.

CURRICULUM VITAE

Guy P.J. Alexandre

PERSONAL

Born:	July 4, 1934
Nationality:	Belgian
Marital Status:	Eliane Moens
Children:	Xavier, Anne, Chantal, Pascale, Brigitte
Office Address:	Department of Renal and Pancreatic Transplantation Cliniques Universitaires Saint Luc 10 Avenue Hippocrate 1200, Brussels, Belgium. 02-7642206

EDUCATION

1952-59	University of Louvain Medical School Louvain, Belgium
1959-61	First and second surgical residency, Department of Surgery (Prof.J.Morelle), Cliniques Universitaires Saint Pierre Louvain, Belgium
1961-62	Graduate C.R.B.Fellow, Research Fellow, Assistant in Surgery Harvard Medical School and Peter Bent Brigham Hospital Boston, Massachussetts
1962-63	Fourth Year surgical Residency, Cliniques Universitaires Saint Pierre Louvain, Belgium

POSITIONS

1963-65	Chargé de Recherches of the Fond National de la Recherche Scientifique of Belgium
1965-72	Associate Chief of Clinics, Department of Surgery Cliniques Universitaires Saint Pierre, Louvain, Belgium
1970-72	Associate Professor of Surgery, University of Louvain Medical School
1976-	Professor of Surgery, University of Louvain Medical School and Chief, Department of Renal and Pancreatic Transplantation and Department of Endocrine Surgery, Cliniques Universitaires Saint Luc Brussels, Belgium

PROFESSIONAL SOCIETIES

International Society of Transplantation
European Society of Surgical Research (founding member)
Société Française de Transplantation
American Society of Transplant Surgeons

European Society for Organ Transplantation (founding member)
Association Française de Chirurgie Endocrinienne
Board of Eurotransplant Foundation

AWARDS

1968	Assubel Prize
1973	Officier de l'Ordre du Mérite de la République Italienne
1977	Commandeur de l'Ordre du Mérite de la République Italienne
1986	Grand Officier de l'Ordre du Mérite de la République Italienne
1989	Huddinge Hospital Transplant Lectureship, Stockholm

HOBBY

Flying: private pilot with IFR qualification

PUBLICATIONS

Total: 227

THE LIFE AND TIMES OF A TRANSPLANT IMMUNOSURGEON

Felix T. Rapaport

Address: Transplantation Service
Department of Surgery
Health Sciences Center
State University of New York at Stony Brook
Stony Brook, New York 11794

Felix T. Rapaport

1966

1991

THE LIFE AND TIMES OF A TRANSPLANT IMMUNOSURGEON

Felix T. Rapaport

> "...How fortunate, indeed, are those who meet the right person at the right time!"
>
> - John Marquis Converse (1)

The Beginning

One of the real pleasures of preparing this manuscript was the opportunity to relive some wonderful memories and to remember some very special people. Crazily enough, this adventure began in 1953, in the A-6 Backroom of the Medical Service (NYU) at Bellevue Hospital in New York City. While serving as a subintern in surgery during my senior medical school year at NYU, I was accidentally inoculated with blood from a patient with severe pancreatico-biliary and liver disease. To the dot, three months later, I had severe jaundice and was admitted to NYU's old Post-Graduate Hospital. I must have been a particularly restless and unreliable patient, because a few weeks later, the Director of Student Health, H. Sherwood Lawrence, transferred me to the A-6 Backroom at Bellevue Hospital. This dungeon, located in the back of the A-6 Medical Ward (NYU), included H. S. Lawrence's office, a relatively large hallway-type area filled with various utensils and equipment, and Lawrence's research laboratory. I spent the next five months flat on my back in this backroom subsisting mainly on Canada Dry cherry soda, frozen strawberries with cream and sugar, and steaks, which were brought lovingly to the A-6 Backroom by my late father and mother every evening after work. My mother would cook the steaks in the ward kitchen, and I would then feast on this food, which was the only nutrition that I could tolerate without vomiting. There is no question that I owe my life to their devoted care and to H. Sherwood Lawrence's tireless and unstinting medical and moral support.

This period was a truly historical one for the development of cellular immunology. In 1953, while I lay in his Backroom, H. Sherwood Lawrence was busily involved in his pioneering studies of transfer factor (the world's first lymphokine) - right next door to my bed! As I began to improve, I became increasingly interested in what he was doing. I began to read and was fascinated by the possibility of applying cell-transfer techniques to transplantation. As time passed it became clear that I would not be well enough to take an internship after graduation. Instead, Lawrence mentioned that one of his colleagues, a plastic surgeon, was trying to establish a collaborative effort for studies of the role of immunology in transplantation. Lawrence asked me whether I might like to act as the liaison with this plastic surgeon for a year and arranged for me to meet John Marquis Converse on February 12, 1954, at the Barbizon Plaza Hotel, where Converse was chairing the First International Conference on Homotransplantation, sponsored by the New York Academy of Sciences. This meeting and that conference set the tone for the rest of my life.

Some of our small band of friends and colleagues of this time are no longer here today. Those of us fortunate enough to survive will never forget the spirit of this first conference. An intrepid handful of individuals from all over the world was present, sharing the ambition to wrest from nature one of its most intimate secrets - the rejection of tissue allografts. At this first conference, Converse had found it relatively difficult to attract many "respectable" immunologists. However, the roster of participants actually reads like a "Who's Who in the History of World Transplantation" (2). The actual title of the conference was "The Relation of Immunology to Tissue Homotransplantation." There was still some uncertainty regarding the causes of allograft rejection. It was the central purpose of the conference to seek an immunological answer to the riddle of graft rejection. The conference opened with a general overview of immunology. Reuben L. Kahn discussed tissue aspects of immunity, while Robert A. Cooke, the founding father of allergy, presented data on allergic responsiveness and the tuberculin reaction. The founding father of modern dermatology, Marion B. Sulzberger, pointed to the resemblance between skin graft rejection and certain skin diseases exhibiting similar localized tissue lysis and destruction. Harry S. N. Greene highlighted his studies of tissue allografts in the anterior chamber of the rabbit eye, and coined some unique terms in the process. Many of us will never forget his claim that, under certain circumstances, the survival of a tissue transplant was a matter of "nurture and not nature." A new art form in adjectives was introduced when Greene noted that a specimen obtained from poultry and transplanted into the eye of a rabbit never lost its "chickenness."

Some now legendary figures contributed to our understanding of rejection. Peter Gorer described his studies of the humoral response to skin allografts in mice, with unique insights which later provided the basis for the discovery of the H-2 system. Pierre Grabar reviewed immunological aspects of graft rejection, and David Pressman discussed the localization of antibodies to various tissues. Morten Simonsen described the development of acquired immunity in canine kidney transplantation, and A. Edward Maumenee presented similar data in corneal transplantation.

The most exciting and challenging aspect of this first conference, however, was the section concerned with attempts to modify host responses to tissue allografts. Nathan Kaliss described the immunological enhancement of tumor allografts and pointed to the capacity of cortisone to intensify this effect. The ability of cortisone to overcome resistance to allografts, and even xenografts, was further documented by Helene Wallace Toolan. It appears remarkable, in this regard, that few reports of the adoption of steroid therapy in clinical transplantation allude to the contributions of these pioneers or to the equally important observations of the Medawar group on this topic.

To this observer, the most timeless paper of this first homotransplantation conference was Billingham, Brent, and Medawar's classical presentation on "Acquired Tolerance to Skin Homografts." This brilliant paper heralded the opening of a new page in transplantation as well as in immunology and continues to play a transcendental role in all of biology, as these findings are now analyzed at a molecular level.

This juxtaposition of questions on the immunological nature of transplantation rejection and the documentation of acquired immunological tolerance, at the same 1954 conference, provide a vivid illustration of the extremely broad spectrum of disciplines and interests which constituted the beginning of an international research effort in transplantation. To this day, biologists and clinicians continue to seek answers to the riddles posed at this first conference. My own transition from a sick bed in the A-6 Backroom at Bellevue Hospital to this conference was an incredibly stimulating challenge. Here was a vast field, ready to be explored, and replete with secrets begging to be uncovered by anyone with the necessary skills and patience. This seemed to be a truly virgin field of endeavor, where the outcome of the experiments did not seem to matter; any question that might be asked would yield new and challenging facts which heretofore were unknown!

Once I attended this conference and met John Marquis Converse, the direction of my life was firmly set. I recently had the sad privilege of writing a reminiscence of this Master, John Marquis Converse, in *The Chimera* (3), and would like to refer the reader to this manuscript for a more adequate acquaintance with this unique Renaissance man. A true aristocrat, of impeccable elegance and graciousness, John Marquis Converse was already an awe-inspiring figure in 1954. An acknowledged leader in plastic surgery, he was devoting much of his time to fostering transplantation research. I introduced myself to him early on the morning of this first conference, and found him to be warm and caring. He warmly welcomed me to his laboratory family and went out of his way for the next two days to introduce me to every one of the conference participants. In 1991, now that world transplantation has assumed awesome and still-growing near-industrial proportions, and research laboratories in the field have proliferated worldwide, it seems strange to recollect that in 1954, all of transplantation consisted, at most, of about 50 daring pioneers. To a great extent, this exponential growth is a product of the vision and commitment of John Marquis Converse, as was expressed so eloquently by Sir Michael Woodruff in his presidential address to the Transplantation Society in 1974 (4). At a personal level, Converse attracted me to the field, nurtured my first naive steps in laboratory experimentation, and remained my closest mentor and friend until his untimely death in 1981.

A Matter of Compatibility

As in so many areas of human endeavor, serendipity has played a major role in many of the quantum leaps which led to today's advanced state-of-the-art in transplantation. It is no small matter of pride to this immunosurgeon that many of these dramatic breakthroughs were provided by operating surgeons. The modern intellectual pendulum is currently succumbing to the temptation of considering that surgeons in full-time academic institutions are mere technicians, expected to generate huge sums of money in their operating rooms, for the support and sustenance of other "truly intellectual and creative" disciplines in medicine. The history of transplantation constitutes a major disclaimer to this philosophical prejudice. Indeed, had it not been for operating surgeons such as Clyde Barker, Folkert Belzer, Hans Brynger, Roy Y. Calne, John Marquis Converse, Joel Cooper, Raffaello Cortesini, W.J. Dempster, Carl Groth, Tekká Hayry, Emile Holman, David M. Hume, Samuel L. Kountz, Rene Küss, William Longmire, Francis D. Moore, Peter Morris, Joseph E. Murray, John S. Najarian, Rudolf Pichlmayr, Paul Russell, Oscar Salvatierra, Ross Sheil, Norman Shumway, Thomas E. Starzl, Michael F.A. Woodruff, and many others around the world, transplantation could never have become the giant discipline that it is today.

After the first conference, I found myself comfortably established in Converse's laboratory at Bellevue Hospital, with a second home in Jerry Lawrence's A-6 Backroom laboratory. The first goal was to demonstrate in definitive fashion in man, as had been shown in the rabbit by Medawar and his associates, that the capacity to recognize allografts resulted in an active immunological response, leading to rejection. A literature search revealed that there were no available objective data regarding the behavior of skin autografts or allografts in man under normal conditions. Earlier studies in humans were related to the placement of skin grafts on burned surfaces and included variables which could render interpretation of experimental grafting extremely difficult. The first required step, therefore, was to develop standardized techniques for the application of small experimental skin allografts to normal body surfaces in human volunteers, for systematic study of the behavior of these grafts, from the time of transplantation to rejection. Parallel autografts in the same recipients served as the controls. After some effort, a standard technique of experimental skin grafts in normal human subjects was developed, and the range of survival of first-set and repeat-set skin grafts was established (5).

The "recall flare" and the "white graft reaction" (6) were described for the first time, and the stage was set for the next phase of the project - ie, documentation of the precise immunological nature of the observed responses. During this phase, a major argument developed among transplantation workers regarding the humoral-versus-cellular nature of allograft rejection. Both hypotheses had strong as well as mutually exclusive proponents. Because of our interest in cellular immune mechanisms, we sought to determine with Lawrence whether skin graft rejection could be mediated in man by leucocyte transfer factor extracts obtained from specifically immunized donors. Volunteers were given first-set skin grafts; within two to three weeks after rejection, they were rechallenged in sequence with a second-, third-, fourth-, and fifth-set skin graft from the same donor. In each instance, the repeat-set skin grafts underwent accelerated rejection. At the height of rejection of the fifth skin graft, leukocytes were extracted and cell-free transfer factor was prepared. The extracts were injected into recipients prior to challenge with skin grafts obtained from the sensitizing donor. Such skin grafts were regularly rejected in accelerated fashion, while concurrent skin grafts from others survived as first-set grafts (7). When skin grafts obtained from the sensitizing donor were placed on recipients, and were then infiltrated *circumferentially* with transfer factor, such grafts also underwent accelerated rejection within 24 to 48 hours, while grafts from other donors, infiltrated with the same transfer factor, were unaffected and continued to survive as first-set grafts (7). These data provided clear-cut evidence of the cellular nature of skin allograft rejection in man (without excluding a possible humoral component in allograft responsiveness). Curiously enough, when the waiting time between allograft rejection and rechallenge with a second-, third-, fourth-, or fifth-set graft was decreased to five to six days, thereby eliciting the white graft reaction in such repeat-set grafts, transfer factor isolated from these subjects failed to confer the capacity to induce allograft rejection.

When subjects used as a source of transfer factor were rechallenged with a skin graft from the same donor on the 90th day following rejection of the last graft from the same source, the grafts were once again accorded first-set survival, and there was no recall flare at the sites of preceding grafts from the same donor. It was concluded on this basis that allograft sensitivity to a particular donor, while generalized, was of relatively limited duration and seemed to persist only as long as a trace of donor antigen(s) remained at the previous graft sites. This notion also provided some reassurance regarding the relatively evanescent nature of the immunological changes produced in recipients of small experimental skin grafts (7).

Pari passu with these experiments, the NYU transplant team pursued studies on the role of leukocytes as a source of alloantigens in man. These studies culminated in the observation that leukocytes could indeed induce strong allograft sensitization and that this capacity was localized to the membrane components of leukocytes (8).

The stage was now set for a remarkable phenomenon of serendipity. After rapid progress in our understanding of the immunology of skin allograft rejection in man since 1954, it seemed imperative to establish definitively the exquisiteness of the individual specificity of the induced immunological responses. For this purpose, recipients were now prepared with skin grafts from one donor; within two weeks after rejection, they were rechallenged with skin grafts from the same donor and from at least four or five other donors. An accelerated rejection limited to second-set grafts from the same donor, versus a first-set rejection of skin grafts from *all other donors* would constitute prima-facie evidence of the exquisite nature of the individual specificity of the induced immunity. To our dismay, however, and in spite of ABO compatibility, one or more first-set skin grafts obtained from "control donors" would invariably undergo the same accelerated rejection reaction accorded to second-set grafts obtained from the sensitizing donor. Since technical factors could be ruled out with confidence, these unexpected results raised the possibility that we might be dealing with "cross-reactions," possibly because of the presence of shared histocompatibility antigens between the sensitizing donors and the donors of first skin grafts that also underwent accelerated rejection. Skin grafts were then exchanged between pairs of individuals who had produced such cross-reactions (putatively sharing histocompatibility antigens) and pairs of subjects who had not elicited such cross-reactions (ie, they did not share histocompatibility antigens). In regularly reproducible fashion, grafts exchanged between donors who were thought to share histocompatibility antigens survived for significantly longer periods than skin grafts exchanged between individuals who did not seem to share such antigens. This 1962 observation (9) is credited with having provided the first experimental demonstration of the existence of tissue or histocompatibility groups in human subjects (10).

Not long thereafter (11), John Marquis Converse met Jean Dausset at a transplantation meeting in Padua, Italy. After exchanging notes, they realized that our two laboratories were actually working on different facets of the same problem, and arrangements were made to have me visit Jean Dausset's laboratory in Paris in 1963. This marked the beginning of a remarkable transatlantic adventure, involving approximately three to four annual commutes from New York to Paris for an extensive analysis of the relationship between Jean Dausset's leukocyte groups and the kind of histocompatibility antigen grouping that had been uncovered in New York by skin graft studies. The awesome skin grafting marathons performed at the Hôpital Saint-Louis in Paris and the relationship of this collaborative effort to our understanding of the HLA system have been described recently by Jean Dausset in his introductory chapter to *The History of HLA*, which has been published in an accompanying volume of this series (10). This adventure has evolved over the years into one of the most prized elements of the writer's existence. Having spent my childhood in Paris, the frequent returns to my home town and the friendship with Jean Dausset, his family, and his Paris staff, and especially the skin graft and blood donor volunteers, constituted a unique human experience. Several panels of these volunteers even came to be studied at the NYU (now Tisch) Hospital and underwent repeated leukopheresis procedures in the 1960s, during our studies of the leukocyte group specificity of allograft sensitization. Jean Dausset and I still speak often of this extraordinary 18-year adventure, which provided the basis for the development of an entirely new page of histocompatibility genetics in transplantation, and now in so many other areas of medicine. During this same period, we were able, in addition, to demonstrate definitively that the ABO erythrocyte antigens are potent alloantigens in man (12) and that human blood platelets lack the capacity to induce allograft sensitivity in human recipients (13) - an intriguing prelude to the later finding that HLA-Class II markers are not expressed on the platelet surface - thus providing a practical adsorption reagent for the isolation of DR-typing antisera.

The Making of an Immunosurgeon

As happens so often in life, most of the events leading to the completion of my training in surgery and in immunology were totally unpredictable. A severe hepatitis led to Lawrence. This was just the beginning. After serving an internship with the late Mark M. Ravitch, at the Mount Sinai Hospital, I returned to NYU, to serve as Lewis Thomas' first research fellow in the Department of Pathology, until called for naval service. With Thomas' help, I was assigned to be the Executive Officer of the United States Naval Medical Research Unit No. 1 at the University of California at Berkeley. There, I was exposed to such giants in microbiology and immunology as Sanford S. Elberg, Charles E. Smith, and Clara Nigg, kindling in me a lifelong love of microbiology. This resulted in the isolation of the endotoxin of Pseudomonas pseudomallei (14) and in the demonstration of the capacity of transfer factor to accord a de novo type of delayed hypersensitivity in naive recipients. In an interesting prelude to my later commuter trips to Paris, Lawrence and I arranged a protocol whereby I would take a naval research team to Bakersfield, California, at the center of the coccidioidomycosis belt in California. We proceeded to isolate large volumes of leukocytes from selected donors at the Houchin Community Blood Bank (Kern County). Each donor had been skin-tested with coccidioidin and had been found to be highly sensitive to this antigen, as a result of earlier contact and/or infection with the causative fungus, Coccidioides immitis, which is endemic to this region of California. I then brought the frozen leukocytes to Bellevue Hospital, where we prepared transfer factor from these cells, and used this material to induce sensitivity to coccidioidin in recipients who had never been exposed to this antigen before (Coccidioides immitis does not occur in New York State). The capacity of the Bakersfield leukocyte extracts to induce sensitivity to coccidioidin in these recipients supported the concept that transfer factor created a state of de novo sensitization in human recipients (15,16).

Upon completion of navy duty, I resumed my surgical training at NYU. Simultaneously, I was a trainee in allergy and infectious diseases, under William S. Tillet and H. Sherwood Lawrence. It was during this time that the first phase of our studies of the sharing of tissue antigens in man was performed. Upon completion of surgical residency, I joined the full-time faculty at NYU, continuing our histocompatibility studies, and extending the interest of our group to other disease states involving alterations in host tissue reactivity. Converse and I became interested in the prolonged survival time accorded to skin homografts after severe thermal injury (17) and showed for the first time that severe thermal injury produced a marked inhibition in the expression of delayed hypersensitivity to tuberculin in experimental animals (18). As a direct spin-off, these studies also led to the original demonstration of the inhibition of delayed hypersensitivity responses in cancer patients (19). In addition, it was shown that thermal injury was associated with significant autoimmune manifestations, and with the development of heterophile antibodies (20,21). An unexpected by-product of the thermal injury studies was the first documentation of mechanisms of pulmonary injury in severe burns - these mechanisms being often associated with microembolization to the lungs, rather than to inhalation injury, as had commonly been assumed (22).

Xenotransplantation and Xenoantigens: The Ubiquity of Mammalian Histocompatibility Determinants in Nature

Along with a number of other authors in this volume, our laboratory has had a persisting fascination with xenograft reactions. After studying the response of mice to rabbit, guinea pig, and rat skin xenografts, it seemed clear that greater or lesser degrees of xenocompatibility were not necessarily related to the actual phylogenetic relationship between donor and recipient (23,24). The response accorded to ABO-specific skin grafts in human recipients sensitized with group-specific A or B substance also appeared to bear a similarity with attenuated forms of xenograft reaction - particularly since these substances were of porcine origin. My earlier interest in microbiology pointed, in addition, to the probability that a wide variety of antigens, both bacterial and mammalian, might be ubiquitous in nature. Dupont had shown as early as 1927 that the so-called natural anti-A and anti-B antibodies were a result of prior ingestion of the appropriate dietary components (25). These findings, strengthened and extended by Georg Springer's classical studies (25), stimulated an on-going preoccupation as to how to apply these possibilities to a transplant model. Once again, the Princes of Serendip took matters into their own hands.

One of my closest friends, Randolph M. Chase, Jr., was serving as a Fellow in Maclyn McCarthy's laboratory at the Rockefeller Institute in the early 1960s. I was very interested in his research project on the biochemical analysis of streptococcal walls and membranes. In the course of an evening's conversation and dinner, we happened to discuss the relationship between Group A streptococcal infection and heart and kidney disease in man. Did it not seem as if the host had actually come to recognize his own kidneys and heart as a homograft, and had then tried to reject these tissues? We pondered over this question for hours, consuming large volumes of banana liqueur (of all things to remember!) and asked ourselves how this hypothesis might be amenable to further experimental analysis. We made no headway, although we somehow felt that the answer was closely within reach. I went to sleep that night with a sense of deep frustration for having failed to resolve this dilemma. I fell asleep and had one of the very few dreams that I have ever been able to remember. In this dream, I was injecting Group A streptococci (the same ones implicated in glomerulonephritis and rheumatic fever) into guinea pigs and then challenging the animals with skin grafts 10 days later. The dream was so vivid that I woke up abruptly at 4:00 a.m., ran to my desk to write down the protocol, and then fell fast asleep again. The very next day, I called Randy Chase, and proposed a collaborative protocol to test the capacity of Group A streptococci to induce skin allograft sensitivity in guinea pigs. This call initiated a decade of intensive studies of the role of bacterial antigens in the induction of allograft sensitivity. After drawing up a detailed protocol, we met with Lewis Thomas and H. Sherwood Lawrence. To our dismay, the idea was not considered to hold very high potential, and Lewis Thomas even told us that if this experiment worked, he would sit down on a stool in our laboratory and cry! With much trepidation, Randy Chase grew some Group A Type 12 streptococci at the Rockefeller Institute, heat-killed the bacterial suspension, and brought it to our laboratory at NYU. We mixed the bacterial cells in Freund's incomplete adjuvant and injected the emulsion into the foot pads of three groups of outbred guinea pigs. A concurrent number of animals received Freund's incomplete adjuvant only, as controls. Two weeks later, the guinea pigs were tested with skin allografts, and about 75 percent of the animals rejected their first-set grafts in an accelerated or white graft manner, as if they had indeed become alloimmunized!

After many repeat experiments to confirm these results, we were allowed to report the information in *Science* in 1964 (26). In short order, it was found that Group A streptococci of all types tested, but no other streptococci, as well as Staphylococcus aureus, shared the capacity to induce allograft sensitivity (27,28). This capacity was localized to the bacterial cell membrane, which could be used in particulate or in solubilized form (29). Further studies showed that Group A streptococcal membrane antisera can induce the passive rejection of skin allografts in guinea pigs (29) and that these antisera can also produce a glomerulonephritis-like lesion after perfusion of kidneys in dogs (30). Streptococci had the capacity to induce allograft sensitivity in every species tested thus far, including mice, rats, rabbits, and guinea pigs. It seemed intriguing, however, that it was not possible to induce accelerated rejection in *all* immunized recipients. In each experiment, a variable number of the outbred recipients, ranging from 60 to 75 percent, exhibited sensitivity - as if the alloantigen(s) cross-reacting with bacterial antigens were distributed in group-like fashion in these outbred species.

More recent studies have shown that the receptor(s) for these streptococcal membrane antigen(s) are located in close proximity to HLA and species-specific antigenic sites on the lymphocyte surface of human cells (31). This finding was particularly intriguing, in view of the observation that human subjects recovering from streptococcal and staphylococcal infection could accord a white-graft kind of rejection to first-set skin allografts transplanted during convalescence (32).

This entire area of research appears to be eminently deserving of further intensive work - with particular regard to its potential relevance to xenotransplantation. It has been one of the writer's most painful regrets that, because of another interest which appeared to have greater clinical applicability, further work on the streptococcal membrane antigens had to be interrupted. I continue to hope and pray that I will return to this fascinating area in the not-too-distant future - particularly in view of the new potent tools of analysis provided by recent advances in molecular biology.

Irradiation, Bone Marrow Transplantation, and Allogeneic Unresponsiveness in Adult Recipients

The philosopher's stone of all transplanters is the search for ways of providing optimum acceptance of organ allografts in adult man without interfering with the remainder of the recipient's defense mechanisms. This goal has generated a large variety of experimental models, with the eventual hope of clinical applicability. A chance meeting with Joseph W. Ferrebee led me unsuspectingly into this path. Some years earlier, Ferrebee and E. Donnall Thomas, who was then Chief of Medicine at the Mary Imogene Basset Hospital in Cooperstown, New York, had established a closely bred colony of beagles for transplantation studies (Cooperstown Colony). They had tried repeatedly to supralethally irradiate the dogs and to reconstitute them by transfusions of bone marrow obtained from a related or unrelated dog. Almost invariably, the grafts failed to take or the animals died of graft-versus-host disease. In one instance, however, during John Mannick's fellowship in Cooperstown, one dog did survive, and when given a kidney allograft from the same donor, it retained normal renal function, after removal of its own kidneys. Ferrebee had been preparing

Felix Rapaport and Jean Dausset (front) at NYU University Hospital in 1967 with four Parisian leukocyte and skin graft donors.

Felix Rapaport capped and gowned for skin grafting in Jean Dausset's office in 1968 (editorial note by Jean Dausset).

leukocyte-grouping antisera and invited us to collaborate with him on a study of the possible influence of these leukocyte groups upon allograft survival. By 1970, the leukocyte antisera prepared by Ferrebee and his associates were shown to have a major influence upon the survival of renal allografts in littermates as well as non-littermate Cooperstown beagles (33). Jean Dausset, who was spending a year of sabbatical in our laboratory in 1970, became intrigued with the Cooperstown Colony, and tracked the DLA genotypes of every member of the colony back to the original 17 founding beagles (34), providing an opportunity to perform further transplantation studies in this colony on the basis of actual DL-A genotypes of each donor and recipient. This advance brought to fruition the long-term dream of performing bone marrow allotransplantation in supralethally irradiated beagles with impunity. Contrary to the experience obtained with randomly selected Cooperstown beagles, or with bone marrow allografts performed between donor-recipient pairs of less well-defined pedigree, this procedure could be completed between genotypically DL-A-identical littermates as well as nonlittermate pairs in the Cooperstown colony in regularly reproducible fashion, without incurring any risks of GvH disease (35). The recipients were also found to be specifically unresponsive to kidney and skin allografts obtained from the marrow donor (35). Further study showed that allogeneic marrow was not necessary for the induction of this type of unresponsiveness. When autologous marrow was extracted from a Cooperstown beagle prior to supralethal total body irradiation, followed by reconstitution with the stored marrow and a renal allograft obtained from a DL-A-identical donor, a significant portion of the recipients became specifically unresponsive to their allografts (36). The working hypothesis was that, in a curious recapitulation of cellular ontogeny, the exposure of rapidly proliferating immature bone marrow cells to alloantigens might have "taught" these cells to recognize such antigens as "self" (36). Later studies identified a class of dendritic cell-like precursors in the bone marrow which appeared to be directly implicated in the mediation of this phenomenon (37, 38). In an attempt to decrease the risks to the host, total lymphoid irradiation techniques have recently replaced the use of supralethal total body irradiation in these experiments, in synergy with other immunosuppressive modalities (39-41). This continues to be one of the most exciting areas in transplantation, particularly as we seem to finally be within reach of this goal in adults, so many decades after Billingham, Brent, and Medawar's classical induction of in-utero allogeneic unresponsiveness.

Clinical Transplantation

By the time Frank Cole Spencer assumed the Chair of Surgery at NYU, the author was well on his way to becoming a super-specialist on 11 mm circular skin grafts in man. Spencer felt it essential to add a clinical dimension to the vast array of immunological and transplantation research available at NYU. He therefore arranged in 1965 for me to spend some time with David M. Hume in Richmond, in the hope of starting a clinical transplantation program at NYU, in partnership with a uniquely skilled urologist, Salah Al-Askari, who had also undergone training in transplantation immunology with Lawrence and Thomas. David Hume and I had been friends for a number of years, prior to my visits to Richmond. At this time, as a mentor, David Hume was tactful, patient, and kind, in surprising contrast to his fiery public image. He was a supremely skilled surgical clinician, who provided a level of emotional support that this "skin grafter" will never forget. The visits to Richmond also exposed me to a unique array of talents, who were all at the Medical College of Virginia with David

Hume at this time. They have all had world-class careers since then. They included H.M. Lee, Peter Morris, Jim Pierce, Mel Williams, and Bill Wolfe. Also present was David Hume's faithful factotum, Gene Pierce, who has since then had a brilliant career as the founding Executive Director of the United Network for Organ Sharing (UNOS).

During this same period, with the support of Jean Dausset's laboratory in Paris, and a stay in New York by Dausset's chief technician, Mademoiselle L. Legrand, we established the East Coast's first histocompatibility testing laboratory, at the Manhattan VA Hospital. This laboratory has steadily progressed since then, and moved en masse to the State University of New York at Stony Brook when I assumed the founding directorship of the transplantation service at that institution in 1977. It continues to be a fully accredited histocompatibility laboratory today, serving the Long Island region. Two of its founding members and colleagues, Mrs. Audrey P. Raisbeck and Mrs. Bjorg Egelandsdal, moved with me to Stony Brook and have continued to render their impeccable level of service. This has been no small feat, in view of the almost incredible proliferation of knowledge of the products of the HLA supergene since 1965!

It is difficult to discuss the beginning of clinical transplantation at NYU without taking note of the early history of hemodialysis at that institution. In the late 1950s, the Professor of Urology at NYU and Bellevue Hospital, the late Robert S. Hotchkiss, had become interested in the life-saving potential of hemodialysis. Except for the pioneering work of Willem Kolff, and the brilliant application of this technique to long-term hemodialysis by Belding Scribner, the prognosis for end-stage renal disease patients was hopeless. Encouraged by Scribner's series of dialysis patients in Seattle, Hotchkiss used his own money to purchase a rudimentary hemodialysis machine, which soon became legendary among Bellevue surgical and urological residents. For a dialysis procedure, all personnel wore boots and aprons, because of the spillage of fluid from the bathtub-like structure which contained the dialysis fluid, in which the drum bearing the dialysis coils was slowly rotated by hand. Hotchkiss supported the concept of transplantation at Bellevue Hospital with enthusiasm. He purchased two much newer dialysis machines, and installed them in the Urology Department at Bellevue Hospital, in order to support the transplantation effort. Salah Al-Askari and the author developed expertise in the installation of Scribner shunts and performed the first long-term hemodialysis procedures at Bellevue Hospital. This was long before the gold rush era of federal support of hemodialysis. Indeed, many of our nephrology colleagues looked upon our hemodialysis activities with suspicion, if not active disapproval; clinical transplantation of kidneys into patients with end-stage renal disease was considered by some of our colleagues to be an inappropriate experimental procedure. Another concern at the time was that a full-fledged program in renal transplantation might eventually limit the number of beds available at University Hospital for paying patients.

In this setting, Al-Askari and I began a clinical transplantation program. One of our earliest patients was a 19-year-old concentration camp survivor with end-stage renal disease. In 1967, she was given a kidney allograft from a cadaver donor who was fully histocompatible with her, on the basis of the prevailing state of the art of tissue typing (donor and recipient shared all three CREGS or cross-reacting groups, "1," "3," and "7"). This patient, who was managed with Imuran and prednisone, following the protocol so brilliantly developed by Thomas E. Starzl in Denver, Colorado, has continued with normal renal function ever since, and we hope to celebrate the 25th anniversary of this transplant in 1992. A memorable aspect of this period of clinical activity was our support cast of surgical residents, who helped us to cover these patients on nights and weekends. These residents were remunerated from John Marquis Converse's plastic surgery funds, and they were a valuable component of the program. One of these surgical residents was Frank Thomas, who currently directs the transplantation program at the East Carolina University in Greenville, North Carolina. His wife, Judith, who was also a protegee of the late David Hume, is today one of the world's leading transplantation immunologists and works closely with Frank in the Greenville program.

Contrary to general opinion, Bellevue Hospital was never a good source of organ donors. There were many deaths in the hospital. These, however, occurred mostly in individuals in poor health, suffering from a wide variety of degenerative and infectious diseases. The ideal organ donors, ie, the younger individuals with good organ function, who had succumbed to major head trauma or cerebrovascular accidents, were in very short supply, and we quickly developed a long waiting list for the few organs which could be retrieved from our home base hospitals. The concept of organ donation was still looked upon with fear and distrust, and progress in developing an effective cadaver donor transplant program was excruciatingly slow. The apparent need of every other medical school in New York City to establish its own transplantation program placed further stress on scarce organ resources. A few living-related donor transplants were performed at NYU, but here again, the prevailing nephrological climate was not altogether supportive, with particular regard to the issue of control of the postoperative care of the transplant recipients.

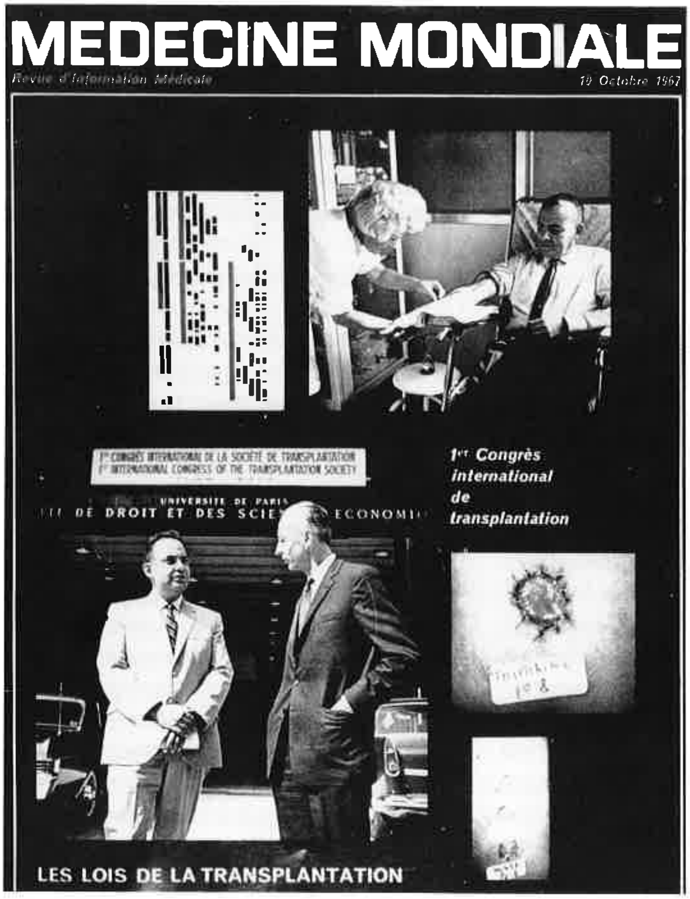
The writer was invited in 1977 to move his entire transplantation team, including the histocompatibility typing facilities, from NYU to the State University of New York at Stony Brook. This opportunity was irresistible, and we transplanted our entire staff, moving into the top floor of the brand-new Health Sciences Center Clinical Tower at Stony Brook. The adjacent University Hospital was still under construction and would not be ready for three years. The interim period provided an opportunity to establish and continue our research program and to secure the necessary official designation as a transplantation center. This was achieved with some effort, in the face of negative testimony to various regulatory agencies by a number of local medical dignitaries, who felt strongly that there was no need for clinical transplantation on Long Island, and that ongoing referral patterns to Manhattan should be preserved. We finally earned the necessary designation and performed the first kidney transplant at Stony Brook in 1981 (a living-related donor kidney transplant). By this time, our team had been enriched by the arrival of Wayne C. Waltzer from a transplant fellowship at the Mayo Clinic. Wayne had been trained in internal medicine, prior to completing a program in urologic surgery at the University of Pittsburgh. He had a special interest in the application of immunological techniques to the study of allograft rejection. A worthy successor to the great Al-Askari, who had opted to remain at Bellevue Hospital, where he is currently the Director of Urology, Wayne has been an integral member of our team ever since. Today, more than 200 kidney transplants later, the Stony Brook program has received recognition as a center of clinical excellence, with first-year kidney and patient survival rates of 85 percent and more than 96 percent, respectively (42). What is even more remarkable is that, in spite of the usual incidence of urological complications following renal transplantation, the Stony Brook program has not lost a single kidney to such complications. This is largely due to Wayne's urological skills. A gifted investigator, he has also received recognition for his study of the cellular events of kidney allograft rejection in man.

The guiding principle of the transplantation center at Stony Brook since its inception has been the key importance of preoperative management and close postoperative follow-up of transplant recipients. This has produced three-year kidney survival rates exceeding 60 percent and five-year survival rates in the 50 percent range (42). Concurrent laboratory study of each patient has also generated close to 120 publications, dealing with various aspects of renal transplantation.

During these years, the writer's attitude toward one particular aspect of renal transplantation has undergone a major change. At the Helsinki Congress of the Transplantation Society in 1986, I was invited to debate the issue of living-donor transplantation with my lifelong friend and colleague, Thomas E. Starzl, for whom I hold deep affection and admiration. Starzl, a towering pioneer in clinical transplantation, had expressed deep misgivings on the use of living donors and, based upon his wide experience, pinpointed some of the cogent reasons why this procedure might not be advisable. I confidently took the opposite side of the issue, and marshalled a cascade of logical arguments to support living-organ donation. More years have now passed, and, as our own team's experience has progressed, I confess that my personal attitude has evolved - at least to the extent that I would not presume today to take the pro side of such an argument under any circumstances! This is not to say that I believe that living-organ donation must be eliminated. I am convinced, however, that such a procedure must be approached with the utmost circumspection, and with a clear understanding of the potential consequences (especially the failure of the transplanted organ in the recipient). Although it is extremely small, the incidence of donor deaths must also be considered and discussed in the greatest detail with each potential donor. Although the cumulative worldwide living-donor mortality is less than one percent, it must not be forgotten that it rises to 100 percent in a donor who has succumbed to his supreme act of generosity. These considerations seem to be at the very least as relevant as the argument of organ scarcity and recipient waiting time, which seem to constitute the primary motivation for living-donor transplantation.

The Transplantation Society

The First International Conference on Transplantation organized under the auspices of the New York Academy of Sciences at the Barbizon Plaza Hotel in 1954, attracted a small band of pioneers (there were fewer than 50 participants), who literally defined the scope of the field and raised almost all of the fundamental questions which continue to occupy transplantation workers today. The impact of this first conference, chaired and organized by the late John Marquis Converse, produced an international ripple effect and led to seven sequential biennial international conferences, held under the same auspices. By the Seventh International Transplantation Conference, held in New York City on February 13-16, 1966, and chaired by John Marquis Converse, Jean Dausset, and the author, a critical mass had been reached, leading to the establishment of a more permanent arrangement for future meetings. The Transplantation Society was founded at the closing session of the Seventh International Transplantation Conference, on February 16, 1966. At this first meeting of the society, a constitution was presented by H. Sherwood Lawrence, Chairman of the Constitutional Committee and was unanimously ratified by the founding members. After a report from the nominating committee, chaired by Jean Dausset, the first slate of officers of the new society was elected by acclamation. D. Bernard Amos, who had been Chairman of the Steering Committee for the establishment of the Transplantation Society, was elected the First Past-Presi-


MEDECINE MONDIALE
Revue d'Information Médicale
19 Octobre 1967
1er Congrès international de transplantation
LES LOIS DE LA TRANSPLANTATION

Front cover of the French edition of World Medical News: First International Congress of the Transplantation Society, with Felix Rapaport and Jean Dausset (lower left) in 1967.

Table 1. A quarter century with the Transplantation Society.

Year	Term of Office	Title	Presiding Officer
1966	4 years	Founding Secretary, Western	Sir Peter Medawar John Marquis Converse Jean Hamburger
1970	4 years	Secretary, Western	Paul S. Russell Sir Michael Woodruff
1974	2 years	Vice-President, Western	Rupert E. Billingham
1976	2 years	President-Elect	Leslie Brent
1978	2 years	President	Felix T. Rapaport
1980	2 years	Immediate Past President	Hans Balner
1982	6 years	Councillor	Paul Terasaki Peter Morris
1986	4 years	Treasurer, Western	Anthony P. Monaco Richard Batchelor
1990	6 years	Councillor	Thomas E. Starzl
1990	6 years	Historian	Thomas E. Starzl

dent of the Society. The other elected officers included:

President:		Sir Peter Medawar
President-Elect:		John Marquis Converse
Vice Presidents:		Georges Mathe Paul S. Russell
Treasurers:		Hans Balner Charles Congdon
Secretaries:		Jean Dausset Felix T. Rapaport
Councillors:	1 Yr:	Jean Hamburger George Klein Gus Nossal Jon J. van Rood
	2 Yrs:	Robert A. Good G. Hoecker Joseph E. Murray D. W. van Bekkum
	3 Yrs:	Ruggiero Ceppellini Milan Hašek H. Sherwood Lawrence Sir M. F. A. Woodruff

Following the election, Sir Peter Medawar assumed the Chair and introduced E. J. Eichwald, who extended to the Transplantation Society the official welcome of the Committee on Tissue Transplantation, Division of Medical Sciences, United States National Academy of Sciences - National Research Council. William Stone then proposed a motion to thank the New York Academy of Sciences for their valuable help and assistance in sponsoring the Seventh International Transplantation Conference. This motion was seconded and unanimously passed by the membership. The next and final order of business was the venue for the First International Congress of the Transplantation Society. After discussion, Paris in the Spring of 1967 was selected unanimously. This marked the close of business of the first meeting of the Transplantation Society.

From these relatively modest beginnings, the writer has been privileged to observe an almost incredible growth in the Society's membership and scope. The Thirteenth International Congress, recently chaired by Oscar Salvatierra in San Francisco, was the largest and most successful transplantation congress ever organized, with over 2,100 registered participants. The forthcoming Fourteenth International Congress, scheduled for Paris in August 1992, promises to be even larger. Our membership has grown from an early handful to over 1,300 physicians and scientists, representing every developed nation in the world; the membership continues to grow at this time. During its history, the Transplantation Society has remained faithful to its central purpose, ie, to provide a common forum for the increasingly divergent disciplines which are now involved in transplantation, with particular reference to a close interaction and cross-fertilization between the clinical and basic sciences. I feel deeply privileged to have had an opportunity to be active on the Council of the Transplantation Society without interruption since February 16, 1966 and to have served in every office of the Society (Table 1). This has been a gift of an almost unbelievable quarter of a century of close contacts with the very finest minds and leadership that our discipline has to offer. It is an experience for which I remain eternally grateful. Beginning as Founding Secretary, in partnership with my friend and co-worker, Jean Dausset, I have had the opportunity to serve the Society as Councillor, Treasurer, Vice-President, and President. My recent appointment as the first Historian of the Society launched me upon a new adventure, of which this chapter is the first product. It is my hope to develop a coherent and fully documented history of our Society and to analyze the trends which have led to its present prominence and international profile. Having witnessed the early modest beginnings, I often have difficulty in understanding how we have reached our current level of sophistication and productivity. One can only hope that, by providing a better understanding of the events of the past, a contribution may be made to the constructive channeling of future efforts, as our early band of survivors continues to be reinforced by thousands of new transplantation recruits, representing an increasingly wide spectrum of clinical and basic sciences.

Transplantation Proceedings

John Marquis Converse, who presided at the Second International Congress of the Transplantation Society in 1968, announced at the Society Council Meeting of that year the establishment of a new journal, *Transplantation Proceedings*, designed specifically to provide for an early and high quality publication of transplantation congresses and symposia, at the lowest possible cost. Jean Dausset was and remains the European editor, and the writer became the founding Editor-in-Chief and continues to hold this position at present. A distinguished and enthusiastic founding Editorial Advisory Board was appointed (43), and the proceedings of the 1968 Congress were published in February 1969, as Volume 1, No. 1 of the new journal. In tandem with the growth of the field, the original size and scope of *Transplantation Proceedings* have undergone considerable development, and each year has seen an increasing demand for space in the journal. After 23 years of publication, *Transplantation Proceedings* is today one of the most often quoted journals in the world biomedical literature and has become a valuable reference source for the transplantation community. *Transplantation Proceedings* has given first priority to in-depth assessments of specialized areas in transplantation. This policy has resulted in the publication of a number of key symposia, which have become classical reference sources. As a result, *Transplantation Proceedings* filled a major void in providing a vehicle for worldwide rapid communication between transplantation physicians and biologists. Today, 23 volumes and tens of thousands of pages later, one can look back with gratitude to John Marquis Converse's early vision and recognition of this future need, and to his active support of the establishment of this journal. John Marquis Converse served as the Founding Chairman of the Editorial Advisory Board until his death in 1981.

Every International Congress of the Transplantation Society since 1968 has graced the pages of *Transplantation Proceedings*; the results speak for themselves. The journal has not missed a single deadline during its existence, and it has succeeded in publishing the congresses, as well as many other key symposia and workshops in record time. As some of my friends and colleagues know, I suffered a cardiac incident requiring open heart surgery shortly after completing the editing of the manuscripts of the 11th International Congress of the Transplantation Society, held in Sydney in August 1988. It should come as no surprise that I devoted most of my "free" time in a coronary care unit and in a cardiothoracic intensive care unit to the correction and checking of the Sydney galley proofs. The same applied to my postoperative convalescence. I owe an eternal debt of gratitude to *Transplantation Proceedings* in helping to preserve my sanity during this very trying period of my life. The Sydney Transplantation Congress, chaired by Ross Sheil, produced the largest set of published reports ever assembled in transplantation, resulting in three enormous and quite heavy volumes. In a way, the timing of this avalanche of manuscripts was perfect, since the author might not otherwise have had the time to truly do justice to his editorial responsibility for the Sydney congress!

Transplantation Proceedings was initially an official publication of the Transplantation Society. Since then, the Editorial Advisory Board, in response to public demand, has recommended that the journal also serve as an official Publication for another 12 affiliated societies, including:

The Japan Society for Transplantation
The European Society for Transplantation
The Hellenic Society for Transplantation
The Canadian Society for Transplantation
The Transplantation Society of Australia and New Zealand
The Scandinavian Transplantation Society
The Latin American Transplantation Society
The Society for Organ Sharing
The Pan-American Society for Dialysis and Transplantation
The Catalan Transplantation Society
The Society of Perioperative Care in Liver Transplant
The Asian Transplantation Society

Additional affiliates are currently under consideration. Generally, local, regional, and national societies which are affiliated with the Transplantation Society, are given priority consideration. In keeping with the long term association of *Transplantation Proceedings* with the Transplantation Society we currently look forward to a further broadening of the scope of the journal, so as to provide better access to the increasing number of symposia, workshops and conferences which reflect ongoing advances in the field. This has been particularly true in the areas of immunosuppression and induction of allogeneic unresponsiveness, where a number of dramatic breakthroughs may be imminent.

Renvoi

The writer deeply appreciates Paul Terasaki's invitation and patient insistence that I *must* contribute a chapter to this volume on the history of transplantation. I confess that I resisted for months this opportunity to record some of my recollections over the years. Indeed, I approached this assignment with the deepest misgivings, because it is so difficult to achieve the delicate balance of looking into the past without sounding self-serving. The approach used in this reminiscence has been to try to remain within the context of the actual occurrences which characterized this period of almost 40 years of unparalleled scientific and clinical ferment. Another dilemma was how to express tactfully one's dismay at the metamorphosis of transplantation. From a relatively cloistered discipline, limited at first to a small band of international acolytes, whose shared interests generated close personal ties, we see today a thriving and flourishing growth industry, involving thousands of participants at various levels. Compared to its modest beginnings, it seems as if much of today's transplantation effort may be driven by motives other than pure scientific inquiry - particularly as transplantation has become a potential cornucopia of clinical practice income. In retrospect, I am grateful for the invitation to relive some unique periods and adventures of my life. To use Lewis Thomas' concept, I have felt like a pirate sailing upon the high seas, seeking to wrest from nature her most tightly kept secrets. One of the particular blessings of the adventure has been to meet and develop friendships with so many other fellow sailors, attracted by the same siren song.

One of the most interesting phenomena of the early days of transplantation was the existence of clusters of talented biologists and physicians around the United States, who shared an interest in the field. The NYU laboratories under John Marquis Converse had special ties to the Boston group, and especially to the late John Merrill and to Joseph E. Murray, who were close friends of Converse and never missed an opportunity to try to beat him at tennis (they did not succeed very often!). We constantly exchanged notes about the experiments in Boston and New York and met with other uniquely talented members of this enclave, including Francis D. Moore, C. Bernard Carpenter, Richard Glassock, and last but not least, Eli Friedman, who subsequently came to the Downstate Medical Center in Brooklyn and gave us an opportunity to perform leukocyte typing for the first renal transplants performed under his leadership in Brooklyn. I have already alluded to David Hume's Richmond group. Another group and its leader, Thomas E. Starzl, began in Denver and went on to ever greater achievement in Pittsburgh. Collaborations with Tom Starzl have had a lasting influence on my life, and I continue to treasure my friendship with this enormously talented and driven genius.

As my great mentor, the late John Marquis Converse, remarked, "How fortunate indeed are those who meet the right person at the right time!" (1). It is remarkable how unexpected accidents of life often become the major determinants of one's fate. A severe, life-threatening hepatitis led me to Lawrence and provided an opportunity to become a link between the immunological approach and John Marquis Converse's skin graft research at Bellevue Hospital. I was uniquely fortunate in enjoying the patient benevolence of a highly supportive and wise Chief of Surgery, the late John H. Mulholland, who understood and encouraged my ambition to continue a research effort during surgical residency. He even went so far as to allow me to serve simultaneously as a surgical resident and as a trainee in allergy and infectious diseases, leading directly to an academic career as an immunosurgeon.

The period of 1957 to 1972 was a rare moment in time for NYU, as well as for world immunology. On one same floor at NYU, there was present during this era an incredible array of world-class immunological talent. How could one fail to be stimulated by the sunshine provided by the likes of Lewis Thomas, Al Stetson, A. M. Pappenheimer, Jr., Colin MacLeod, B. Benacerraf, Jonathan Uhr, Zoltan Ovary, Peter Miescher, Robert McCluskey, Edward Franklin, Marvin Kuschner, Leon Sokoloff, and so many others, who were available to all comers, at all times! These were unbelievably heady days, where a veritable mecca of world immunology was congregated in one finite and highly supportive environment. One wonders how this rare community of unbelievably talented immunologists could ever have coexisted, and one cannot help but mourn the circumstances which caused this now legendary assemblage to be scattered to all corners of the United States and Europe.

This era was indeed the right time for transplantation, and NYU was one of the right places, providing a setting in which the search for the secrets of nature was a joy and happiness, rather than just hard work. In this context, one must refer to another mecca, the Buffalo School of Immunology, founded by the late Ernst Witebsky, and led by my lifelong friend, the great Felix Milgrom. They and their brilliant associates of the time put the concept of autoimmunity on the experimental and clinical map. The unswerving friendship and support of the Buffalo group and their representative in our NYU laboratories, Kyoichi Kano (one of my first fellows), constituted an additional source of inspiration, and led to a number of fascinating collaborative experimental studies in thermal injury, as well as in transplantation.

The events leading to the Paris commuter adventures have already been noted. The long-term John Marquis Converse-Jean Dausset-Felix Rapaport partnership was a logical continuum of our efforts of the preceding decade. It seemed in 1963 as if all of the previous work had only been a preparation for the next two decades. This effort has clearly been one of the highlights of my life, not to speak of the resulting close lifelong kinship among our families. Jean

Dausset is a truly unique individual, whose restless creativity and search for new facts, as well as his almost psychic intuition and views into the future, have been an everlasting source of joy and inspiration. No career or record of achievement ever occurs in a vacuum. At the close of this reminiscence, I wish to place on record my immense debt of gratitude for the faithful inspiration, guidance, and support of the three individuals (outside of my beloved late parents) who were most directly responsible for whatever I may have achieved: John Marquis Converse, H. Sherwood Lawrence, and Jean Dausset.

Mottoes

Considered an affectation by some, mottoes have great usefulness in expressing with economy of words the basic principles which govern human behavior. They also tell a great deal about the basic attitudes of the individual who selects a particular motto as a guidepost. My existence has been influenced deeply by three mottoes, acquired from diverse sources. The first, "Tuhe recht und scheue niemand," belongs to Mr. Max W. Rapaport, my beloved late father ("Do justice and fear noone."); the second, "Keep on path," is a sign which was displayed prominently in H. Sherwood Lawrence's laboratory for many years; and third, "Vouloir pour valoir," is the motto of Jean Dausset's laboratory ("One must want something totally in order to achieve worthiness."), and became our joint motto for the HLA adventure. What better conclusion to this reminiscence than to recall these meaningful words!

ACKNOWLEDGMENTS

It is not possible to end this reminiscence without acknowledging the support, encouragement, and skilled assistance provided by a number of key technical and administrative staff members, who habitually worked way above and beyond the line of duty to achieve our common goals. Over the years, some names stand out, particularly those who have remained with me over many years of faithful and loving collaboration, at NYU and at Stony Brook. On the technical side, I will never forget my first technician, Arlene Zisman, who provided the nucleus for a rapidly growing laboratory at NYU, or Juan Grullon, master of all trades, who worked with us at NYU and followed the group to Stony Brook. In the same category, Arthur Miller and Arturo Quel constituted the backbone of our experimental surgical laboratory activity, and deserve much gratitude for their patient and highly skilled help and assistance. Audrey P. Raisbeck and Bjorg Egelandsdal were part of the founding tissue typing team at NYU, and remain with us to this day at Stony Brook, ably assisted by Chris Pullis. On the administrative side, two faithful and unbelievably skilled partners deserve particular recognition. These are Alice Brzytwa, who was my first secretary, and over the years became the Chief of Staff of an ever growing activity. When we moved to Stony Brook, Alice Brzytwa could not follow us for personal reasons. Her role was assumed by Mrs. Mavis Stephenson, who had joined our group in 1969 at NYU, and has been our administrative and spiritual leader at Stony Brook. When we moved to Stony Brook, Mrs. Stephenson took over the administration of our entire program and continues to do so in her impeccable and gracious way. Mrs. Stephenson has attended all of the Transplantation Society Congresses since 1976, and has become internationally known and admired by the entire transplantation community because of her outstanding service as the perennial Coordinator of the Transplantation Proceedings Congress Office. To a very large extent, the rapid and well-organized publication of the proceedings of each congress has been a result of her tireless labors and enthusiasm. She is a widely ad-

mired figure in world transplantation and deserves a particular vote of thanks for her selfless devotion. The addition of a clinical component to our program at Stony Brook constituted a new dimension and required the establishment of a new effort - organ procurement. The names of Dr. Joel S. Sherlock, Ms. Winnie Mack, the late Brian Reilly, and our current Chief Transplant Coordinator, Stephen Hurley, and his associate Stephen Knapik, deserve special mention in this regard. They are but a few of the key valued associates and support personnel who have made it possible for this author and his collaborators to function productively over the years. The author is grateful to have this opportunity to express to all of them his deepest admiration, appreciation, and affection. Last but foremost in my heart and mind, I must mention the one partner and soulmate without whom I would never have survived, my beloved wife and co-pilot, Margaret, who has shared so many of these experiences over the years. Her love, faith, and steadfast partnership have been the central sunshine of my existence, and have allowed me to weather the numberless crises which are such a regular part of the human experience.

REFERENCES

1. Converse JM. Peripatetics of an Immunosurgeon. Transplant Proc 1975, 7:ix.

2. Miner RW, Ed. The relation of immunology to tissue homotransplantation. Ann NY Acad Sci 1955; 59:277.

3. Rapaport FT. A reminiscence: John Marquis Converse - renaissance man and founding father of transplantation. The Chimera 1990; 2:11.

4. Woodruff MFA. Presidential Address. Transplant Proc 1975; 7:vii.

5. Converse JM, Rapaport FT. The vascularization of skin autografts and homografts: an experimental study in man. Ann Surg 1956; 143:306.

6. Rapaport FT, Converse JM. The immune response to multiple-set skin homografts: an experimental study in man. Ann Surg 1958; 147:273.

7. Lawrence HS, Rapaport FT, Converse JM, Tillet WS. Transfer of delayed hypersensitivity to skin homografts with leucocyte extracts in man. J Clin Invest 1960; 39:185.

8. Rapaport FT, Dausset J, Converse JM, Lawrence HS. Biological and ultrastructural studies of leucocyte fractions as transplantation antigens in man. Transplantation 1965; 3:490.

9. Rapaport FT, Lawrence HS, Thomas L, et al. Cross-reactions to skin homografts in man. J Clin Invest 1962; 41:2166.

10. Dausset J. The HLA adventure. In: Terasaki PI, Ed. History of HLA: Ten Recollections. UCLA Tissue Typing Laboratory, Los Angeles, 1990; 1.

11. Converse JM. Experimental human skin allografts, the HLA complex, and a Nobel Prize. Plast Reconstr Surg 1982; 70:255.

12. Rapaport FT, Dausset J, Legrand L, et al. Erythrocytes in human transplantation. effects of pretreatment with ABO group-specific antigens. J Clin Invest 1968; 47:2206.

13. Dausset J, Rapaport FT. Transplantation antigen activity of human blood platelets. Transplantation 1966; 4:182.

14. Rapaport FT, Millar JW. The endotoxic properties of pseudomonas pseudomallei. Arch Pathol 1961; 71:429.

15. Rapaport FT, Lawrence HS, Millar JW, et al. Transfer of delayed hypersensitivity to coccidioidin in man. J Immunol 1960; 84:358.

16. Rapaport FT, Lawrence HS, Millar JW, et al. The immunologic properties of coccidioidin as a skin test reagent in man. J Immunol 1960; 84:368.

17. Rapaport FT, Converse JM, Horn L, et al. Altered reactivity to skin homografts in severe thermal injury. Ann Surg 1964; 159:390.

18. Rapaport FT, Converse JM. Alterations in immunological responsiveness associated with severe thermal injury. In: Wallace AB, Wilkinson AM, Eds. Research in Burns. Edinburgh, E. & S. Livingstone, Ltd., 1966; 407.

19. Solowey AC, Rapaport FT. Immunologic responses in cancer patients. Surg Gynecol Obstet 1965; 121:756.

20. Rapaport FT, Sampath A, Kano K, et al. Immunólogical effects of thermal injury. I. Inhibition of spermatogenesis in guinea pigs. J Exp Med 1969; 130:6.

21. Kano K, Milgrom F, Witebsky E, Rapaport FT. Immunologic studies in thermal injury: hemagglutinating factor in the lymph of burned rats. Proc Soc Exp Biol Med 1966; 123:930.

22. Rapaport FT, Nemirovsky MS, Bachvaroff R, Ball SK. Mechanisms of pulmonary damage in severe burns. Ann Surg 1973; 177:472.

23. Ben-Hur N, Solowey AC, Rapaport FT. The xenograft rejection phenomenon. I. Response of the mouse to rabbit, guinea pig and rat skin xenografts. Israel J Med Sci 1969; 5:1.

24. Ben-Hur N, Solowey AC, Rapaport FT. The xenograft rejection phenomenon. II. Responses of the guinea pig to mouse, rat, and rabbit skin xenografts. Israel J Med Sci 1969; 5:3.

25. Rapaport FT. The biological significance of cross-reactions between histocompatibility antigens and antigens of bacterial and/or heterologous mammalian origin. In: Kahan BD, Reisfeld RA, Eds. Transplantation Antigens, Markers of Biological Individuality. New York, Academic Press, 1972; 81.

26. Rapaport FT, Chase RM Jr. Homograft sensitivity induction by Group A streptococci. Science 1964; 145:407.

27. Chase RM Jr, Rapaport FT. The bacterial induction of homograft sensitivity. I. Effects of sensitization with Group A staphylococci. J Exp Med 1965; 122:721.

28. Rapaport FT, Chase RM Jr. The bacterial induction of homograft sensitivity. II. Effects of sensitization with staphylocci and other microorganisms. J Exp Med 1965; 122:733.

29. Rapaport FT, Markowitz AS, McCluskey RT. The bacterial induction of homograft sensitivity. III. Effects of Group A streptococcal membrane antisera. J Exp Med 1969; 129:623.

30. Rapaport FT, Markowitz AS, McCluskey RT, Hanaoka T. Induction of glomerulonephritis in renal autografts. Surgery 1969; 66:34.

31. Rapaport FT, Bachvaroff R, Markowitz AS. Lymphocyte surface effects of soluble extracts of streptococcal membranes (TGCM). I. Relationships between HLA and species-specific antigenic sites and TGCM receptor sites. J Immunol 1973; 110:1058.

32. Roses D, Zabriskie J, Rapaport FT. White graft reaction after streptococcal and staphylococcal infection in man. Transplant Proc 1973; 5:487.

33. Rapaport FT, Hanaoka T, Shimada T, et al. Histocompatibility studies in a closely-bred colony of dogs. I. Influence of leucocyte group antigens upon renal allograft survival in the unmodified host. J Exp Med 1970; 131:881.

34. Dausset J, Rapaport FT, Cannon FD, Ferrebee JW. Histocompatibility studies in a closely-bred colony of dogs. III. Genetic definition of the DL-A system of canine histocompatibility, with particular reference to the comparative immunogenicity of the major transplantable organs. J Exp Med 1971; 134:1222.

35. Rapaport FT, Watanabe K, Cannon FD, et al. Histocompatibility studies in a closely-bred colony of dogs. IV. Tolerance to bone

marrow, kidney and skin allografts in DL-A identical radiation chimerae. J Exp Med 1972; 136:1080.

36. Rapaport FT, Bachvaroff RJ, Mollen N, et al. The induction of unresponsiveness to major transplantable organs in adult mammals - a recapitulation of ontogeny by irradiation and bone marrow replacement. Ann Surg 1979; 190:461.

37. Rapaport FT. Supralethal total body irradiaton and reconstitution with autologous marrow for the induction of specific allogeneic unresponsiveness in the adult host. In: Slavin S, Ed. Tolerance in Bone Marrow and Organ Transplantation. The Netherlands, Elsevier/North Holland Biomedical Press B.V., 1984; 385.

38. Rapaport FT, Arnold AN, Asari H, et al. Implication of Ia-positive bone marrow interstitial stem cells in the induction of unresponsiveness to canine renal allografts. Cell Immunol 1987; 104:255.

39. Rapaport FT, Meek AG, Arnold AN, et al. Preoperative preparation of high-risk specifically hyperimmunized canine renal allograft recipients with total lymphoid irradiation and cyclosporine. Transplantation 1987; 44:185.

40. Rapaport FT, Meek A, Miura S, et al. Synergistic effects of combined immunosuppressive modulation. I. Unresponsiveness to dendritic cell-depleted renal allografts in dogs exposed to total lymphoid irradiation. Transplantation 1988; 45:682.

41. Rapaport FT, Meek AG, Hayashi R, et al. Immunosuppressive strategies for the induction of unresponsiveness to canine renal allografts. Transplant Proc 1989; 21:381.

42. Shabtai M, Waltzer WC, Anaise D, et al. Relevance of the center effect to the utilization of scarce resources for renal transplantation. Transplant Proc 1991; 23:1882.

43. Advisory Board. Transplant Proc 1969; 1:683.

CURRICULUM VITAE

Felix Theodosius Rapaport

PERSONAL

Born: September 27, 1929; Munich, Germany

Citizenship: United States

Office Address:
Department of Surgery, Transplantation Service
State University of New York at Stony Brook
Health Sciences Center
Stony Brook, New York 11794-8192

EDUCATION

1947	Stuyvesant High School, New York
1951	New York University-Washington Square College, A.B.
1954	New York University School of Medicine, M.D.

POSITIONS

1954-55	Post-Doctoral Fellow in Medicine and Surgery, New York University
1955-56	Intern in Surgery, the Mount Sinai Hospital, New York
1956	Post-Doctoral Fellow in Pathology, New York University
1956-58	Executive Officer, U.S. Naval Medical Research Unit No. 1 Department of Bacteriology, University of California at Berkeley
1958-61	U.S.P.H.S. Trainee in Allergy and Infectious Diseases NIH Training Program at New York University
1958-61	Assistant in Medicine, New York University Medical Center
1958-62	Assistant Resident, Resident and Chief Resident in Surgery NYU Surgical Divisions, Bellevue and University Hospitals
1961-62	U.S.P.H.S. Career Development Award National Institute of Allergy and Infectious Diseases
1961-62	Instructor in Surgery, New York University Medical Center
1962-65	Assistant Professor of Surgery, New York University Medical Center
1962-77	Attending Surgeon, University Hospital, NYU Medical Center
1962-77	Director of Research, Institute of Reconstructive Plastic Surgery New York University Medical Center
1962-77	Visiting Surgeon, Third and Fourth (NYU) Surgical Divisions Bellevue Hospital, New York
1964	Fellow, American College of Surgeons
1965-71	Associate Professor of Surgery, New York University Medical Center
1965-77	Director, Transplantation and Immunology Division Department of Surgery, New York University Medical Center
1971-77	Professor of Surgery, New York University Medical Center

1977-	Senior Attending Surgeon and Chief, Transplantation Service SUNY at Stony Brook, Stony Brook, New York
1977-89	Professor and Deputy Chairman, Department of Surgery SUNY at Stony Brook, Stony Brook, New York
1978-	Professor of Pathology (Immunology), Department of Pathology SUNY at Stony Brook
1989-	Director, Residency Training Program in Surgery SUNY at Stony Brook, and Affiliated Hospitals
1989-	Surgeon-in-Chief, University Hospital, Stony Brook
1989-	Professor and Chairman, Department of Surgery SUNY at Stony Brook, Stony Brook, New York

PROFESSIONAL SOCIETIES

	American Surgical Association
	Alpha Omega Alpha
	Society of University Surgeons
	New York Surgical Society
	New York Academy of Sciences
	International Society of Experimental Hematology
	American Association of Immunologists
	Reticuloendothelial Society
	Council of Biology Editors
	American Society of Transplant Surgeons
	American Society of Transplant Physicians
	American Association of University Professors
	American Society for Histocompatibility and Immunogenetics
	Society of Surgical Chairmen
	Association of Surgical training Program Directors
1966-91	The Transplantation Society (Founding Secretary, Vice President, President Elect, President, Councillor, Treasurer, Historian)
1989-92	Pan-American Society for Dialysis and Transplantation (Councillor)
1967-	American Surgical Association
1984-85	New York Regional Transplant Program, Inc. (President)
1985-88	United Network for Organ Sharing (Board of Directors)

AWARDS

1961-62	U.S.P.H.S. Career Development Award National Institute of Allergy and Infectious Diseases
1963-72	Career Scientist Award, Health Research Council of the City of New York

1963-79	Guest Investigator, Insitut de Recherches de la Faculte de Medicine, Universite de Paris, Centre George Hayem (Dr. Jean Dausset) Paris
1970	Ordre National du Mérite (France)
1979	Gold Medal of the City of Paris
1979	Gold Medal of the Société d'Encouragement au Bien, Paris
1981	Grand Croix des Palmes Academiques (France)
1987	Claude Bernard Visiting Professor of Experimental Medicine, College de France, Paris
1989	First Samuel L. Kountz Award, Howard University
1990	Officer of the Legion of Honor (France)
1990	Lester Hoenig Award, National Kidney Foundation of New York, New Jersey
1990	Samuel A. Berson Medical Alumni Achievement Award for Clinical Science, New York University

ADVISORY COMMITTEES

1964-68	Advisory Committee on Collaborative Research in Transplantation and Immunology, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland
1968-72	Member, Arthritis and Metabolic Diseases Program Projects Advisory Committee, Division of Research Grants, NIH, Bethesda, Maryland, Chairman 1971-72
1969-71	Committee on Clinical Transplantation, National Research Council - National Academy of Sciences, Division of Medical Sciences
1972-76	Scientific Advisory Board, National Kidney Foundation
1974-77	Merit Review Board in Immunology, Veterans Administration Department of Medicine and Surgery, Medical Research Service, Washington, D.C.
1974-78	American Institute of Biological Sciences Advisory Panel on Medicine and Dentistry to the U.S. Office of Naval Research
1975-79	Member, Surgical Study Section B, Division of Research Grants NIH, Bethesda, Maryland
1975-79	Scientific Advisory Board, American Cancer Society
1984-87	Renal Disease Advisory Committee, State of New York Department of Health, Office of Health Systems Management

INTERNATIONAL MEETINGS

1964/1966	Co-Chairman, Sixth and Seventh International Conferences on Tissue Transplantation, New York Academy of Sciences, New York City
1968	Co-Chairman, Second International Congress of the Transplantation Society, New York City
1976	Co-Chairman, Sixth International Congress of the Transplantation Society, New York City

EDITORIAL BOARDS AND EDITORSHIPS

Transplantation Proceedings (Founding Editor-in-Chief 1968-)
Journal of Kidney Diseases (Associate Editor 1981-86)
Transplantation (Editorial Board 1968-72)
Journal of Craniofacial Genetics and Developmental Biology (Editorial Board 1982-86)
Disease Markers (Editorial Board 1982-)
Cellular Immunology (Editorial Board 1983-)

PUBLICATIONS AND BOOKS

Total: 475

1968	Human Transplantation, Grune and Stratton (with Jean Dausset)
1969	Transplantation Today, Grune and Stratton, New York (with John Marquis Converse)
1971	Transplantation Today, Grune and Stratton, New York (with Hans Balner and D.W. van Bekkum)
1972	Tissue Typing Today (with Jean Dausset)
1972	Artificial Organs and Cardiopulmonary Support Systems, Grune and Stratton, New York (with John P. Merrill)
1973	Transplantation Today, Grune and Stratton, New York (with Hans Balner and Samuel Kountz)
1973	Clinical Transplantation, Grune and Stratton, New York (with David M. Hume)
1973	A Second Look at Life, Grune and Stratton, New York
1975	Transplantation Today, Grune and Stratton, New York (with Michael Schlisinger and Rupert Billingham)
1975	David M. Hume Memorial Symposium on Transplantation, Grune and Stratton, New York (with W. Lawrence, Jr., H.M. Lee, R.R. Lower, J.M. Pierce, and J.S. Wolfe)
1977	Transplantation Today, Grune and Stratton, New York (with John Marquis Converse

1979	Transplantation Today, Grune and Stratton, New York (with Raffaello Cortesini)
1981	Transplantation Today, Grune and Stratton, New York (with Anthony P. Monaco and Mary L. Wood)
1983	Transplantation Today, Grune and Stratton, New York (with Leslie Brent, John Fabre, Michael W. Elves, and Robert A. Sells)
1984	Angioaccess: Principles and Practice, Grune and Stratton, New York (with Wayne C. Waltzer)
1985	Transplantation Today, Grune and Stratton, New York (with John S. Najarian, Fritz H. Bach, David E.R. Sutherland)
1987	Transplantation Today, Grune and Stratton, New York (with Pekka Hayry and Saija Koskimies)
1989	World Transplantation, Appleton and Lange, Connecticut (with A.G.R. Sheil)
1991	World Transplantation, Appleton and Lange, Connecticut (with Oscar Salvatierra and Nancy Ascher)

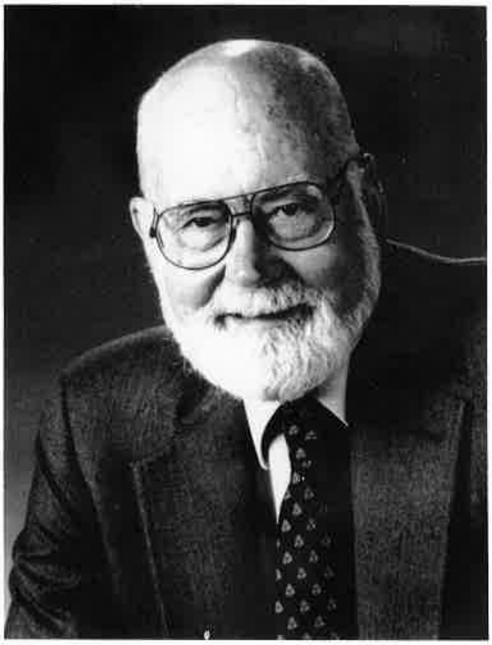
ALLOGENEIC MARROW GRATING:
A STORY OF MAN AND DOG

E. Donnall Thomas

Address: Fred Hutchinson Cancer Research Center
1124 Columbia Street
Seattle, Washington 98104

E. Donnall Thomas

1946



1990

ALLOGENEIC MARROW GRAFTING - A STORY OF MAN AND DOG

E. Donnall Thomas

By the time I graduated from medical school in 1946 I had become interested in hematology. In 1947 I was one of Clement Finch's first hematology fellows at the Brigham Hospital in Boston. In 1950, after returning from military service, I took a post-doctoral year at MIT with Dr. John Loofborough to work on stimulating factors released from irradiated yeast as a prelude to working on factors that might stimulate bone marrow growth. In 1949 Jacobson and colleagues reported that a mouse could be protected from otherwise lethal irradiation by shielding the spleen and shortly thereafter Lorenz, C. Congdon, and D. Uphoff showed that irradiation protection could be conferred by an intravenous injection of marrow cells. These reports attracted my attention because at that time it was assumed that protection against irradiation was due to humoral factors stimulating marrow recovery, since it was well known that transplantation of tissues or cells from one individual to another was impossible because of the "barrier" that had been described by Alexis Carrel.

In 1951 I returned to the Brigham Hospital, first to complete my clinical training and then to serve as staff hematologist. During that time I was well acquainted with Joe Murray and, for a short time, helped care for his first twin recipient of a kidney graft. That experience stimulated my interest in transplantation, but my own work was concerned with developing methods for working with bone marrow and for studying marrow metabolism.

In the early 1950s Burnet's hypothesis and Medawar's experiments had attracted a great deal of interest and indicated that the transplantation "barrier" of Carrel might not be totally insurmountable. In 1955, Main and Prehn published a paper showing that mice protected from lethal irradiation by marrow infusion would accept a skin graft from the donor strain, an observation strongly suggesting that a transfer of living donor cells had occurred to account for the apparent tolerance. In the same year, Ford and colleagues used cytogenetics to show the presence of donor cells in irradiated mice protected from lethal irradiation by a marrow infusion.

In the summer of 1955, my family and I moved to Cooperstown, N. Y., to the Mary Imogene Bassett Hospital, at the invitation of Dr. Joseph Ferrebee, whom I had known during our time in Boston together. When I arrived in Cooperstown, I found that Joe also had been following the experiments of Medawar, Jacobson, Lorenz, R.T. Prehn, and Ford and their co-workers. There followed much discussion of these experiments, sometimes in the laboratory, sometimes while riding Joe's horses around the hills of Cooperstown. In the autumn of that year, we began studies of marrow transplantation while continuing my studies of marrow metabolism. It seemed that marrow transplantation might be relatively easy in human patients with malignant disease, especially leukemia, because of the immunosuppressive properties of the disease and its treatment. Therefore, we decided to begin cautious exploration of marrow grafting in patients. At the same time we started studies of marrow grafts in the dog, a species commonly used for transplantation research. We reasoned that the dog would be suitable for studies designed to transfer knowledge of transplantation biology from inbred murine models to outbred species while also tolerating clinical procedures comparable to those used for human patients.

Joe Ferrebee, Don Thomas, James Bordley, III, Cooperstown in 1956.

John Mannick with recipient and donor of both marrow and kidney, Cooperstown in 1958.

Honest John, male beagle, first long-term survivor of a marrow graft from a female littermate, Cooperstown in 1958.

The years in Cooperstown, 1955 to 1963, were a most interesting time. I served as Physician-in-Chief of the hospital, an affiliate of Columbia University. The pleasant summers and cold winters of that upstate New York rural community were conducive to the conduct of research in a low key environment. Joe and I received enthusiastic support from Dr. James Bordley, III, the director of the hospital as well as from Dr. Otto Sahler, radiologist. We began to attract some bright, hard-working young Fellows: first, Harry Lochte, Jr. and then Shinpei Kasakura, William (Buck) Greenough, III, Ted Hager, Emory Herman, Jr., John Mannick, Reginald Clift, D. A. Henderson, and J.A. (Lex) Cavins. Ted Graham became our principal animal technician and we relied heavily on the expert knowledge of Dr. James Baker of the Veterinary Virus Research Institute at Cornell.

Very quickly we found that allogeneic marrow grafts in human patients were going to be difficult indeed to achieve. In our first paper published in the *New England Journal of Medicine* in 1957, we described only one transient graft of donor marrow. We did find that we could infuse rather large amounts of properly prepared marrow intravenously without ill effect, and we pointed out the potential application of marrow grafting to the treatment of diseases of the marrow, to irradiation accidents, and to solid organ grafting. In 1959 we reported our first two identical twin marrow transplants for patients with far advanced acute lymphocytic leukemia. We showed that an intravenous infusion of syngeneic marrow readily restored marrow function after supralethal total body irradiation, but in both patients leukemia recurred in a few months. We did discuss approaches to eradication of leukemia, including transplantation in remission and the use of allogeneic marrow to achieve an antileukemic effect. Interestingly, 15 years were to go by before we were able to transplant allogeneic marrow for patients with leukemia in remission.

We put a great deal of effort into studies of the canine model. We quickly found that dogs could routinely survive three to four times the lethal dose of irradiation if given an autologous marrow graft and that canine marrow could be cryopreserved in glycerol or DMSO for months or years. Allografts, however, were quite a different problem. Most recipients of allogeneic marrow died either from graft failure or from graft-versus-host disease and its complications. Postgrafting administration of methotrexate as an immunosuppressive agent, as first suggested by Delta Uphoff, delayed the onset and severity of graft-versus-host disease but still most dogs died. However, we noted that an occasional dog given a marrow graft from a donor of opposite sex survived the graft-versus-host disease period and became a long-term survivor with no further treatment. Blood genetic markers confirmed the presence of donor marrow. These survivors indicated to us that marrow grafts could be successful, and our problem was to find the factors underlying success or failure.

At that time the Bassett Hospital was not equipped for a large dog program. As our results improved we had more and more canine survivors which we wanted to observe for months or years. Since we lived on a 70 acre farm five miles from Cooperstown, it seemed that we could easily construct some runs and care for the dogs there. My wife agreed but finally rebelled when we had some 50 dogs frisking about the place.

In the days before satellites and the FAX machine revolutionized communication, discussion and collaboration were very dependent on personal interaction. Those experimental studies in Cooperstown began to attract attention, and soon this small village a long way from the nearest center of academic medicine received a stream of eminent physicians and scientists from the far reaches of the globe. We benefited greatly from these discussions and the names of these visitors form a roster of those who have made major contributions to modern medicine. The visitors included Ugo Carcassi, Gene Cronkite, Ruggero Ceppellini, Louis Diamond, Clement Finch, Ted Fliedner, Marylou Ingram, Vera Haskova, Pancho Hoecker, Lionel Israels, H.E.M. Kay, George Mathe, John Merrill, David Nathan, Pablo Rubenstein, Paul Russel, Scott Swisher, Fred Stohlman, Leandro Tocantins, Sime Vlahovic, and Michael Woodruff. Some of our visitors may not recall their trip with much enthusiasm. There was no airport, and the nearest bus stop was 15 miles away. They had to solve the problem of getting there by hitch-hiking the last few miles. Dr. and Mrs. Mathe visited during a winter storm. The evening social event was a dinner party at our home, an old farm house, charming but isolated. The road, even in summer, was best negotiated in a four-wheel drive vehicle. In a foot of snow it became a challenge. At one point we skidded, made a 180 degree turn and were forced to back the way down the last hill. Somehow this seemed to be inappropriate for our Parisian visitors.

The University of Washington School of Medicine came into being at the end of the 1940s and the early faculty included many friends from Boston, especially Clem Finch and Robert Williams. Rob was the first Chairman of the Department of Medicine. He envisioned a great school of medicine but recognized the problems of geographic separation in the Pacific Northwest. He wanted to include all the major institutions in greater Seattle as equal partners in the University sphere. He approached me about joining the faculty and going to the United States Public Health Service Hospital. The attractions of the developing scientific environment, my old friends, and the beautiful Pacific Northwest led to our decision to move. In the summer of 1963, my family and I and Ted Graham and his family moved to Seattle. We were joined by Bob Epstein who had planned to move from Chicago to Cooperstown but made a 180 degree turn to go to Seattle.

Georges Mathe, Dirk van Bekkum, George Santos, Don Thomas, Charles Congdon, Delta Uphoff, New York in 1968.

With grant support from the NIH and NCI and with the moral support of Rob Williams, we remodeled space in the Public Health Service Hospital and made a dog laboratory and irradiation facility in an unused former military facility in West Seattle. Research fellows who came to work with us over the next few years included Rainer Storb, Dean Buckner, Paul Neiman, Alex Fefer, and Reginald Clift, all of whom are still my colleagues in charge of major programs in their own sphere of interest.

We concentrated our efforts on studies of transplantation in the canine model. These studies carried us into studies of immunology, transplantation biology, irradiation biology, infectious diseases, and supportive care including platelet and granulocyte transfusions. The knowledge of human tissue typing had progressed rapidly during the 1960s, but we were almost alone in trying to develop canine typing sera. With the advice of Rose Payne, Jon van Rood, and Bernard Amos, we finally developed typing sera that enabled us to identify "matched" donor-recipient pairs of canine littermates. The recipient given supralethal irradiation and a marrow graft with postgrafting immunosuppressive therapy with methotrexate almost always became a long-term survivor in contrast to death from graft-versus-host disease when the littermate donor was "mismatched." These studies convinced us that it should be possible to carry out grafts between "matched" human siblings.

Our first such attempt in 1965 ended in disaster. The patient was a child with end-stage leukemia who had an identical twin and several other siblings. We reasoned that we might find a matched allogeneic donor among the nontwin siblings and be able to fall back on the syngeneic donor if necessary. Bernard Amos and his technician came to Seattle with their battery of partially characterized human typing sera. Typing of the family indicated one sibling whose cells reacted concordantly with the patient. We admitted the patient to the Clinical Research Center at the University of Washington Hospital. Following 1000 rad of total body irradiation, the patient was given the allogeneic graft from the sibling and postgrafting methotrexate. The patient died on the 12th day of a bacteremia due to an organism that was found to be growing in the water pitcher on the bedside table. This experience convinced us that we should not undertake an allogeneic graft except in a facility designed and staffed for care of immuno-incompetent patients with no bone marrow function.

We wrote a grant application which included remodeling at the Public Health Service Hospital for single isolation rooms, our own dedicated nursing staff, and appropriate support facilities. The grant was site-visited late in 1967 and funded in early 1968. We completed the remodeling and began to recruit and train our nursing team. In November of 1968, Bob Good and his colleagues carried out the first allogeneic marrow transplant from a sibling selected by histocompatibility typing for a child with an immunologic deficiency disease. We carried out our first such transplant for an adult with leukemia in March of 1969. These studies began the "modern" era of human marrow transplantation.

Initially we had eight beds at the United States Public Service Health Hospital. Patients received total body irradiation from the dual cobalt-60 radiation sources in the dog laboratory in West Seattle. I have the greatest admiration for those early patients who were irradiated there. The facility was totally underground, dark, and gloomy. Many of the dogs were housed there for their follow-up period. As the patient was carried down into the radiation area all of the dogs would begin to howl, thinking it was feeding time. To the patient it must have been something comparable to a descent into hell.

In 1972, the United States Public Health Service Hospital was threatened with

Don Thomas, George Santos, Ted Graham, Seattle in 1969.

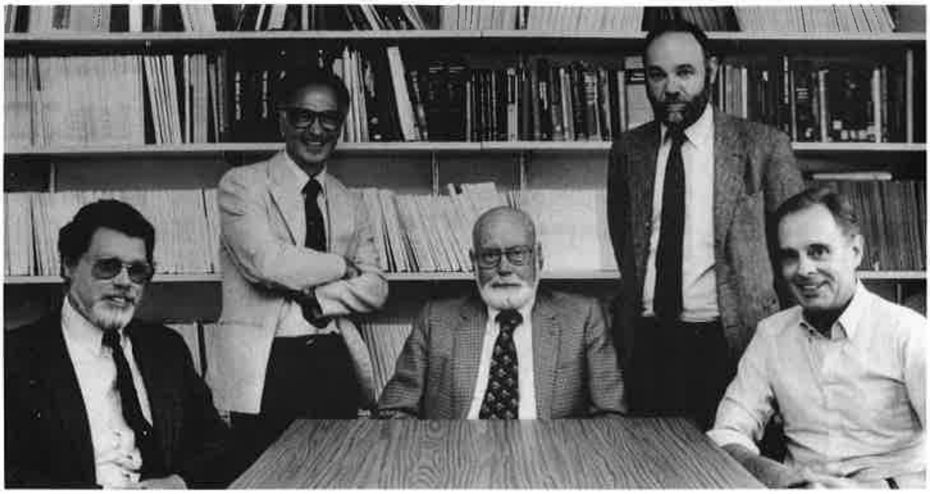
Karel Dicke, Dirk van Bekkum, J.E. Till, J.P. O'Kunewick, Charles Congdon, Don Thomas, Lyle Heim, John Trentin, Georges Mathe, Lyle Sensenbrenner, George Santos, Mortimer Bortin, Houston in 1974.

closure, and we moved to Providence Hospital where we had 14 beds. In 1975 we moved to the newly constructed Fred Hutchinson Cancer Research Center where we had 20 beds and a new dual cobalt-60 radiation facility. In 1985 Swedish Hospital Medical Center made available an additional 40 beds. Our laboratory facilities and our staff increased concomitantly. In 1976, John Hansen joined our team as Head of the Human Immunogenetics Program and succeeded me as Associate Director of the Clinical Division in 1989. Currently, more than 50 faculty members representing many different disciplines are members of the team.

Our coordinated multidisciplinary work has, above all, been fun because of the intellectual challenges. There was and is an atmosphere on the transplant team for challenging biologic "truths," for opening new pathways, and a willingness to take risks when necessary. We learned the need for a dedicated team of workers which extended far beyond the physicians themselves. Nurses, technicians, animal care personnel, and support staff were all important. Without animal studies, none of this work would have been possible. Moreover, we were inspired by those courageous patients who were willing to take some risks to try for a new approach when all of the conventional therapy only offered short-term benefits.

The 1970s and 80s have been characterized by an increasing number of marrow transplant centers, an increasing number of malignant and nonmalignant disease categories suitable for allogeneic marrow grafting, and an increasing number of long-term survivors who appear to be cured of their disease. Most recently large numbers of unrelated marrow donors of known HLA type have been enlisted in the United States and several other countries so that more and more often we are able to find an unrelated donor for a patient in need. In many instances marrow grafting is now cost-effective when compared to conventional therapy. Current research points the way to further improved results. The last four decades have provided exciting scientific challenges in patient-related research, and it appears that the next decade will continue that tradition.

These are, of course, personal recollections and are not intended to be comprehensive. Citation of the work of so many others who contributed to the field will be found in the reference section.



Paul Neiman, Alex Fefer, Don Thomas, Dean Buckner, Rainer Storb, Seattle in 1988.

Dean Buckner and Reginald Clift in Seattle, 1989.

John Hansen, Don and Dottie Thomas, Robert Day, Stockholm, 1990.

The doctors Don Thomas, Sr. and Jr. at the Mulchatna River in Alaska, 1986.

Don and Dottie Thomas in Boston, 1944.

Don and Dottie Thomas in Stockholm, 1990.

REFERENCES

1. Thomas ED, Lochte HL, Jr., Lu WC, Ferrebee JW. Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. N Engl J Med 1957; 257:491.

2. Thomas ED, Ashley CA, Lochte HL, Jr., et al. Homografts of bone marrow in dogs after lethal total-body radiation. Blood 1959; 14:720.

3. Thomas ED, Lochte HL, Jr., Cannon JH, et al. Supralethal whole body irradiation and isologous marrow transplantation in man. J Clin Invest 1959; 38:1709.

4. Epstein RB, Storb R, Ragde H, Thomas ED. Cytotoxic typing antisera for marrow grafting in littermate dogs. Transplantation 1968; 6:45.

5. Storb R, Epstein RB, Graham TC, Thomas ED. Methotrexate regimens for control of graft-versus-host disease in dogs with allogeneic marrow grafts. Transplantation 1970; 9:240.

6. Thomas ED, Storb R, Clift RA, et al. Bone-marrow transplantation. N Engl J Med 1975; 292:832, 895.

7. Thomas ED, Flournoy N, Buckner CD, et al. Cure of leukemia by marrow transplantation. Leuk Res 1977; 1:67.

8. Neiman PE, Reeves W, Ray G, et al. A prospective analysis of interstitial pneumonia and opportunistic viral infection among recipients of allogeneic bone marrow grafts. J Infect Dis 1977; 136:754.

9. Buckner CD, Clift RA, Sanders JE, et al. Protective environment for marrow transplant recipients. A prospective study. Ann Intern Med 1978; 89:893.

10. Hansen JA, Clift RA, Thomas ED, et al. Transplantation of marrow from an unrelated donor to a patient with acute leukemia. N Engl J Med 1980; 303:565.

11. Fefer A, Cheever MA, Greenberg PD, et al. Treatment of chronic granulocytic leukemia with chemoradiotherapy and transplantation of marrow from identical twins. N Engl J Med 1982; 306:63.

12. Hansen JA, Anasetti C, Beatty PG, et al. Treatment of leukemia by marrow transplantation from HLA incompatible donors. Effect of HLA-disparity on GVHD, relapse and survival. Bone Marrow Transplant 1990; 6:108.

13. Clift RA, Buckner CD, Appelbaum FR, et al. Allogeneic marrow transplantation in patients with acute myeloid leukemia in first remission. A randomized trial of two irradiation regimens. Blood 1990; 76:1867.

14. Thomas ED: Bone marrow transplantation - past, present and future. The Nobel Prizes, 1990, The Nobel Foundation, Stockholm, Sweden.

CURRICULUM VITAE

E. Donnall Thomas

PERSONAL

Born:	March 15, 1920; Mart, Texas
Marital Status:	Married, Dorothy Martin; 3 children

EDUCATION

1937-41	University of Texas, Austin, Texas, B.A.
1941-43	University of Texas, Austin, Texas, M.A.
1943-46	Harvard Medical School, Boston, Massachusetts, M.D.

POSITIONS

1946-47	Internship in Medicine, Peter Bent Brigham Hospital Boston,Massachusetts
1947-48	Research Fellow in Hematology, Peter Bent Brigham Hospital Boston, Massachusetts
1948-50	U.S. Army, assignments in internal medicine
1950-51	National Research Council Postdoctoral Fellow in Medicine, Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts
1951-53	Chief Medical Resident and Senior Assistant Resident Peter Bent Brigham Hospital, Boston, Massachusetts
1953-55	Instructor in Medicine, Harvard Medical School Boston, Massachusetts Hematologist, Peter Bent Brigham Hospital, Boston, Massachusetts Research Associate, Cancer Research Foundation Children's Medical Center, Boston, Massachusetts
1955-63	Physician-in-Chief, The Mary Imogene Bassett Hospital Cooperstown, New York
1955-63	Associate Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University, New York, New York
1963-90	Professor of Medicine, University of Washington School of Medicine, Seattle, Washington
1963-85	Head, Division of Oncology, University of Washington School of Medicine, Seattle, Washington
1974-	Member, Fred Hutchinson Cancer Research Center, Seattle, Washington
1974-89	Director, Medical Oncology, Fred Hutchinson Cancer Research Center, Seattle, Washington

1982-89	Associate Director, Clinical Research Programs, Fred Hutchinson Cancer Research Center, Seattle, Washington
1990-	Professor Emeritus of Medicine, University of Washington School of Medicine, Seattle, Washington

BOARD CERTIFICATION

1953	American Board of Internal Medicine

PROFESSIONAL SOCIETIES

	American Association for Cancer Research
	American Association of Physicians
	American Federation for Clinical Research
	American Society for Clinical Oncology
	American Society of Clinical Investigation
1987-88	President, American Society of Hematology
	International Society of Experimental Hematology
	International Society of Hematology
	National Academy of Sciences
	Society for Experimental Biology and Medicine
	Swiss Society of Hematology
	The Transplantation Society
	Western Association of Physicians
1965-69	Hematology Study Section, National Institutes of Health
1969-73	Board of Trustees Leukemia Society of America, Inc. Medical and Scientific Advisory Committee
1970-74	National Cancer Institute Clinical Cancer Investigation Review Committee

AWARDS

1974	First Annual Eugene C. Eppinger Lecture at Peter Bent Brigham Hospital and the Harvard Medical School
1975	A. Ross McIntyre Award, University of Nebraska Medical Center
1975	The Henry M. Stratton Lecture, American Society of Hematology, Dallas
1977	The Lilly Lecture, Royal College of Physicians, London
1979	The Philip Levine Award, American Society of Clinical Pathologists, New Orleans
1980	American Cancer Society Award for Distinguished Service in Basic Research
1981	Kettering Prize of the General Motors Cancer Research Foundation for contributions to the diagnosis and treatment of cancer

1981	Honorary Doctorate of Medicine, University of Cagliari, Sardinia
1981	Special Keynote Address Award, American Society of Therapeutic Radiologists
1982	Stratton Lecture, International Society of Hematology
1982	Paul Aggeler Lecturer, University of California, San Francisco
1983	David A. Karnofsky Memorial Lecturer, Annual Meeting of the American Society of Clinical Oncology
1983	Robert Roesler de Villiers Award, Leukemia Society of America
1984	Sixty-fifth Mellon Lecturer, University of Pittsburgh School of Medicine
1985	Stanley Wright Memorial Lecturer, Annual Meeting of the Western Society for Pediatric Research
1987	Karl Landsteiner Memorial Award, Annual Meeting of the American Association of Blood Banks
1989	Elected Corresponding Member, Academie Royale de Medecine de Belgigue
1990	Terry Fox Award, Canada
1990	Gairdner Foundation International Award
1990	North American Medical Association of Hong Kong Prize
1990	Nobel Prize in Medicine
1990	Presidential Medal of Science

EDITORSHIPS AND EDITORIAL BOARDS

1962-75/1977-82	Blood
1970-76	Transplantation
1974-81	Proceedings of the Society for Experimental Biology and Medicine
1977-	Leukemia Research
1982-	Hematological Oncology
1982-	Journal of Clinical Immunology
1985-	American Journal of Hematology
1986-	Bone Marrow Transplantation

PUBLICATIONS

Total: 892

BONE MARROW TRANSPLANTATION: A STORY OF STEM CELLS

Dirk W. van Bekkum

Address: Radiological Institute TNO
Box 5815
2280 HV Rijswijk
Lange Kleiweg 151
Rijswijk, The Netherlands

Dirk van Bekkum

In office, 1960

Presented with steering wheel for water ski boat at retirement as Director of Radiobiological Institute.
1990

BONE MARROW TRANSPLANTATION: A STORY OF STEM CELLS

Dirk W. van Bekkum

Introduction

After the second world war, many of the liberated European countries organized their defense research activities, among them the Netherlands. During my military service as an army doctor, I was commissioned to work at the newly founded Medical Biological Laboratory of the Defense Research Organization TNO. TNO stands for the Dutch Organization for Applied Research. During my medical studies I had become fascinated with biochemistry and as a British Council Scholar I had worked one year under Sir Rudolph Peters in the Biochemical Department at Oxford. Therefore, I was delighted when the director of the Medical Biological Laboratory suggested that I join its small Radiobiology Department to study the effect of irradiation on oxydative phosphorylation in mitochondria of various tissues. And, yes, my first contribution to the literature on radiation biology had to do with biochemical alterations in irradiated organs.

However, this did not last for long. Within a year after my appointment, the radiologist who was heading the department resigned. I was offered his position and the task of initiating a comprehensive program in radiobiological research, including chemical protection and biological therapy of radiation sickness. Thus, in the early fifties we joined the small number of people who were studying the treatment of lethally irradiated rodents with cell suspensions from bone marrow or spleen: Charles Congdon at the Biololgical Division of Oak Ridge National Laboratory, Leonard Cole, Ed Alpen, and Peter Nowell at the United States Naval Radiological Defense Laboratory, and John Loutit and Charles Ford at Harwell.

At that time I had developed a strong motivation to go into cancer research, but I could not find an outstanding place that suited my purpose. In the long run, radiation biology seemed to offer enough opportunities to satisfy my oncological interests. After all, ionizing radiation was already known to induce cancer, and radiotherapy was a fast developing and powerful tool in the treatment of malignancies. Therefore I accepted the offer and became, among other things, involved in bone marrow transplantation.

In 1955 the concern about the fallout from nuclear test explosions as well as the growing applications of radioactive isotopes and nuclear energy caused our government to decide that the radiobiology department of the Defense Research Laboratory was too limited in size and scope to serve the needs of the country. The Health Division of TNO was charged with the organization of a radiobiological institute and funds were provided for the construction of a new laboratory, complete with radiation sources, all sorts of isotope handling facilities, and an animal breeding colony. I was invited to organize this new research group and to design the new laboratory. In 1960, when the building was nearly completed, I was appointed its director and moved in with a group of about 20 people who had been assembled in the mean time. In 1970, additional constructions doubled the laboratory space to house a large Van de Graaf neutron generator, a modern SPF mouse and rat breeding colony, and ample facilities for breeding rhesus monkeys and chimpanzees.

The bone marrow transplantation program spanning more that 30 years produced a tremendous spin-off into immunology, immunosuppression (from total body irradiation to antilymphocytic serum), organ, skin and nerve transplants in rodents, dogs and monkeys; into experimental hematology with the isolation of the pluripotent stem cells as the main target; and into leukemia research. Our experimental radiotherapy was expanded to include experimental chemotherapy, immunotherapy, and hyperthermia, because radiation was no longer being used as the sole therapeutic modality in the treatment of cancer. Thus, there was plenty of opportunity to pursue my interest in cancer research.

As the emphasis of the work of TNO is on application, which by the way is the objective of every medical researcher, I had many opportunities to collaborate with clinical colleagues, mainly at the University Hospitals of Leiden and Rotterdam and at the Daniel den Hoed Cancer Hospital in Rotterdam. I was part of the group, who along with George Mathé, Henry Tagnon, Ted Fliedner, Laszlo Lajtha, and others, founded the "Groupe Européenne de Chemotherapie Anticancereuse" in 1960, (later renamed European Organization for Research and Treatment of Cancer (EORTC)) which has developed into the largest international clinical trials enterprise in oncology. During my tenure of a Fogarty Scholarship at NIH in 1975, I had an opportunity to study the system and organization of the United States Comprehensive Cancer Centers (CCC) and afterwards was able to introduce this system into my own country. Since 1977 I spent part of my time as Executive Director of the CCC which serves Rotterdam and the surrounding area as well as the province of Zeeland, comprising a population of two million with 24 participating hospitals. This also allowed me close interaction with clinical oncology activities.

These various positions brought me into contact with the best scientists and clinicians from a variety of disciplines. I was called upon to participate on the boards of their societies and the organizing committees of their scientific meetings. All these encounters enrich one's scientific and social experience. Because of these very diverse developments of my interests, it can be said with Dr. Pangloss (1) that I have had the best of all possible worlds. My adventures in science have been more that I could describe in a few pages and I am not yet ready to write my memoirs.

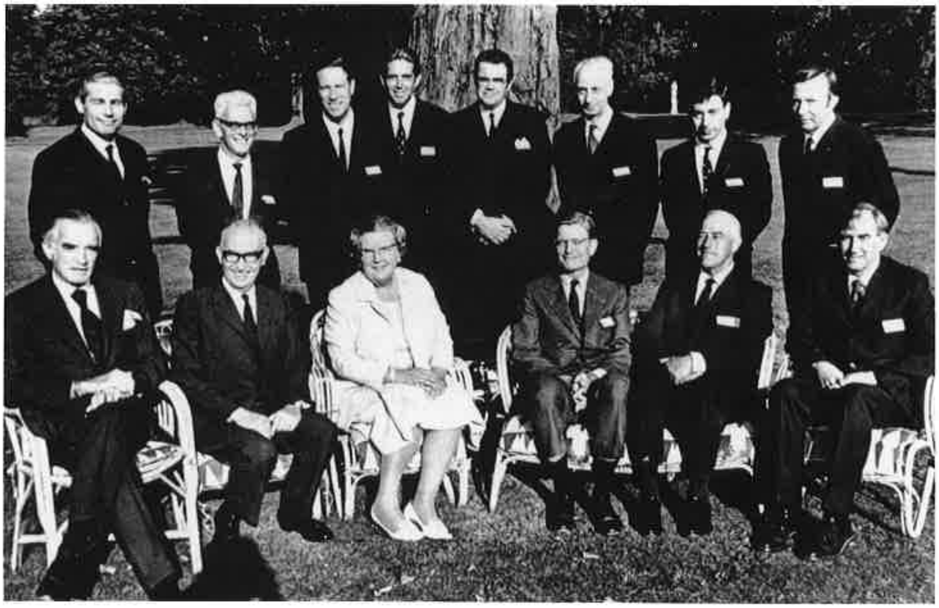
Therefore I have chosen to contribute a poem to this volume entitled "The Ballad of Cmomc" (2), a term we used in our first paper that identified the pluripotential hemopoietic stem cell in enriched bone marrow cell preparations (3).

"The Ballad of Cmomc" was written in 1990 on the occasion of the Symposium Panorama Stem Cell which was organized in my honor in Rotterdam, when I reached the official retirement age at the university. In this poem I attempted to express my deep gratitude to the speakers and the organizers. The Ballad is also a tribute to the scientists who were closely associated with me for shorter or longer periods during more than 30 years of hemopoietic stem cell research and its diverse applications.

The verses allude to highlights of that research. For the present occasion and for the benefit of the uninitiated reader, I have added notes to clarify the several rather obscure artistic interpretations.

1. Voltaire, FMA. "Candide," 1759.
2. "Cell meeting our morphological criteria."
3. VanBekkum DW, VanNoord MJ, Maat B, Dicke KA. Attempts at identification of hemopoietic stem cell in mouse. Blood 1971; 38:547.

With Laszlo Lajtha (left) and Peter Koller, 1960.



Queen Juliana of the Netherlands with officers and members of the organizing committee of the Transplantation Society, Third International Transplantation Congress in the Hague, September 1970.

First Was the Chimaera

Chimaera was the creature's name
That was for Cmomc to blame.
With Davids, Weyzen and with Otto Vos
We could establish that its marrow was
Repopulated by the donor's progeny
To grow with stroma host in perfect harmony.
Thus marrow grafting was accepted
As the mechanism that protected
From supralethal TBI
*Even before there was an RBI. **

We started experiments on the treatment of radiation sickness in 1952. At that time, the beneficial effects of injecting hemopoietic cell suspensions into lethally irradiated mice and guinea pigs, as first demonstrated by Jacobsen (1) and Lorenz (2), had not been explained. Most investigators favored the idea of a humoral factor that would stimulate hemopoietic regeneration. Not bad, in view of the impressive effects now seen from some of the hemopoietic growth factors. The humoral factor theory was supported by observations that cell-free extracts of bone marrow had therapeutic properties and also by the curative action of rat bone marrow in lethally irradiated mice. The latter finding provided a particularly strong argument against the transplant mechanism, as–even at that time–it was known that xenogeneic tissue grafts were always rejected. Few people understood that high-dose total body irradiation is an exceptionally strong immunosuppressive regimen. Nevertheless, it was necessary to test both options and this could be done best by identifying the cells of the hemopoietic tissues in the recovered animals. In the case of a humoral mechanism, one would expect host type cells; in the case of a graft, one should be able to demonstrate the presence of donor type cells.

In Rijswijk we worked on this interesting problem with Jan Davids, Otto Vos, and Walter Weyzen. We were not familiar with the cytology of rodent hemopoiesis since there was hardly any literature on the subject. We were lucky to receive help from Paul Lopez Cardozo, the famous cytologist, who spent many hours with us over May Grunwald-stained smears of mouse bone marrow, patiently translating his vast knowledge of human bone marrow cells to the mouse. We developed three different methods of distinguishing host type from donor type cells: serological, histochemical, and a retransplantation assay based on the fact that one needs about 20 times more bone marrow cells for protection with allogeneic than with syngeneic marrow. Our results, which proved reconstitution of the rescued animals with donor type cells, were published in March 1956 (3). In the same month, similar results obtained with karyotyping were reported by Ford, et al (4) and, using alkaline phosphatase staining to distinguish rat granulocytes from mouse granulocytes, by Nowell, et al (5). Thus, the radiation chimera was born. We could not foresee the enormous impact that radiation chimeras were going to have on immunology and hematology. But we were duly impressed by the unexpected implications of our discovery. It seemed that a relatively small number of donor cells could be transplanted and then, in their new host, give rise to the complete scala of hemopoietic mature cells, continuing to do so for the rest of the life of the animal. In the years to follow, the number of different cell types that became identified as donor derived in radiation chimeras and therefore as descendants of the hemopoietic stem cells, continued to increase. Nearly every new addition was another sensation, eg, the sessile macrophages in the skin and the liver, the dendritic cells in the thymus, the B and T lymphocytes (not yet invented at the time the chimera was discovered), and the osteoclast. The concept of the radiation chimera changed the current thinking about hemopoiesis as being polyphyletistic and the idea of a common pluripotential mother cell being functional during adult life began to emerge.

---

*Radiobiological Institute

1. Jacobsen LO, Marks EK, Gaston EO. Effect of mouse embryo tissue on survival of irradiated mice. In: Brues AM, Ed. Quart Rep of Research. Argonne National Laboratory AML-4625. February, March, and April, 1951; 46.
2. Lorenz E, Uphoff DW, Reid TR, Shelton E. Modification of irradiation injury in mice and guinea pigs by bone marrow injections. J Natl Cancer Inst 1951; 12:197.
3. Vos O, Davids JAG, Weyzen WWH, vanBekkum DW. Evidence for the cellular hypothesis in radiation protection by bone marrow cells. Acta Physiol Pharmacol Neerl 1956; 4:482.
4. Ford CE, Hamerton JL, Barnes DWH, Loutit JF. Cytological identification of radiation chimeras. Nature 1956; 177: 452.
5. Nowell PC, Cole LJ, Habermeyer JG, Roan PL. Growth and continued function of rat marrow cells in X-radiated mice. Cancer Res 1956; 16:258.

Participants in International Symposium on Bone Marrow Therapy and Protection in Irradiated Primates held at Rijswijk, 1962.

The Approach of Cmomc

It was Till and McCullough who did away
With the microscope by their spleen colony assay.
Nowell, Trentin and many others
Proved that the colony forming cells are the mothers
Of all the blood and lymphatic cells,
Thus tolling for good and forever the bells
On polyphyletism
As the hemopoietic mechanism.

The introduction of the spleen colony assay (1) added substantially to the stem cell option because it allowed quantition and thereby the study of the kinetic aspects of damage and recovery. The key results to support the concept of a pluripotential hemopoietic stem cell were, of course, the demonstration that one spleen colony could contain erythroblasts, myeloid cells, and megakaryocytes as well as cells that could give rise to secondary colonies; the fact that by employing specific chromosomal markers, it was shown that all the cells of one spleen colony were the progeny of a single cell; and, finally, the finding that the progeny of a single colony could reconstitute the whole hemolymphopoietic system of a lethally irradiated mouse (2). However, not until 1970 was there convincing demonstration with unique chromosomal markers that lymphocytes and myeloid cells were derived from the same precursor cell (3). Although in later years evidence for the existence of lineage-restricted precursor cells with extensive self-renewal capacity has been brought forward (4), the existence of the pluripotential stem cell has been generally accepted by hematologists and immunologists. These discoveries also helped to prepare the way for considering graft versus host disease (GvHD) following allogeneic bone marrow transplantation as the result of graft-derived lymphocytes reacting against host tissues.

1. Till JE, McCulloch EA. A direct measurement of the radiation sensitivity of normal mouse bone marrow cells. Radiat Res 1961; 14:213.
2. Trentin JJ, Fahlberg WJ. An experimental model for studies of immunologic competence in irradiated mice repopulated with "clones" of spleen cells. In: Conceptual Advances in Immunology and Oncology, 16th Annual Symposium (1962), Texas, Harper and Row, New York, 1963; 66.
3. Nowell PC, Hirsch BE, Fox DH, Wilson DB. Evidence for the existence of multipotential lympho-hematopoietic stem cells in the adult rat. J Cell Physiol 1970; 75:151.
4. Abramson S, Miller RG, Phillips RA. The identification in adult bone marrow of pluripotent and restricted stem cells of the myeloid and lymphoid systems. J Exp Med 1977; 145:1567.

Cmomc In Hiding

This made immunologists pay some attention
To secondary disease and its prevention.
Rem Petrov and Veljko Stankovic
Were succeeded by Ledney and Boranic.
From Italy came Guiseppe Tridente
To become Karel Dicke's primo assistente.
And Haim Ginsburg in between bicycle rides
Made T lymphocytes poison each other on slides.
Bill Crouch was the one with the monkey connection
Who helped us to found the primate collection.
For our preclinical experimentation
We selected man's closest relation.
With VanPutten in charge of our monkey clinic
The whole operation went just like a picnic.

This verse relates to the period between 1960 and 1970. As soon as the facilities of the newly established Radiobiological Institute were available, we started work with rhesus monkeys. We invited Bill Crouch, a radiobiologist who had been working on the physiology of monkeys with Overman in Memphis, Tennessee, to help us set up a primate colony in Rijswijk. We were able to carry out basic studies in that species on the radiation-induced bone marrow syndrome and the protective effects of autologous and allogeneic bone marrow and fetal liver (1). This was before the days of MHC typing and the main lesson was the extreme severity and lethality of GvHD in monkeys, much more severe that what we had seen in rodents. Our pathologist, Marco de Vries (2), made the first comprehensive description of GvHD lesions in monkeys and later in human material with George Mathé in Paris who had grafted the first small group of leukemic children with bone marrow (3). At that time, Loek van Putten, the Associate Director of the Institute who was specialized in internal medicine, also took an interest in bone marrow transplantation, as it was evident that this treatment modality had great potential for application. And we were joined by Hans Balner who had trained at the Memorial Sloan Kettering Institute in New York. Hans began his career in Rijswijk by studying GvHD in rats. Thereafter he concentrated on monkeys and became Director of the Primate Center in 1970. During the second half of the sixties, after having tried all the known immunosuppressive agents on GvHD, we participated in the antilymphocyte serum boom. Preparing, purifying, and testing these sera became an important activity for several years, and test systems involving about any other tissue besides bone marrow were set up and exploited in rats and monkeys.

This decade also saw the beginnings of HLA typing. With the help of Jon van Rood in Leiden, that principle was introduced into all the transplantation work with rhesus monkeys. Through this development, the colony at Rijswijk became the only large primate center with a fully MHC-typed population.

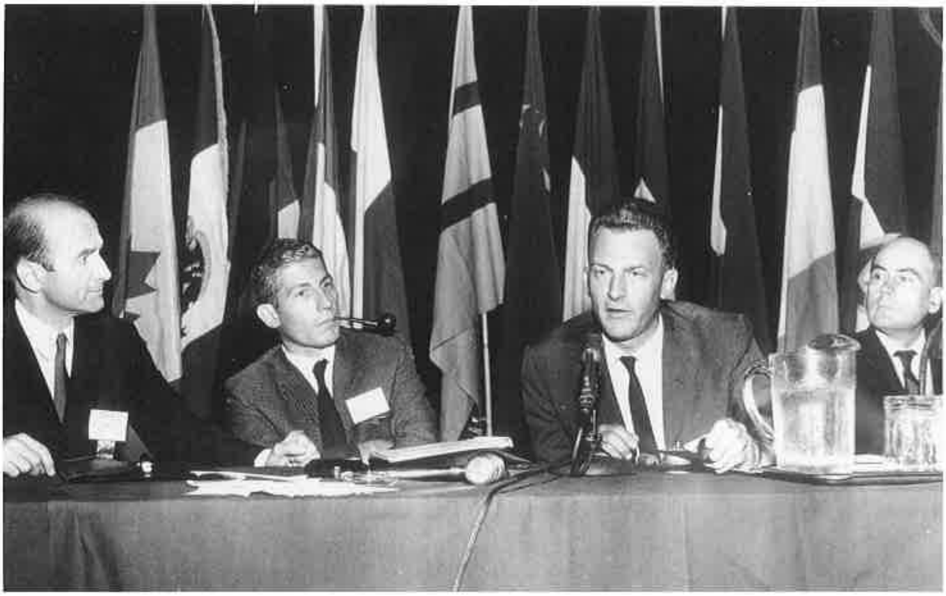
Rem Petrov from the USSR and Stankovic from Belgrade spent time at the Institute studying the immunological aspects of chimerism. Tridente from Italy and Haim Ginsberg from Israel were pursuing their ideas on the possibilities of anti-lymphocytic serum to modify activities of lymphocytes in vitro and in vivo. David Ledney, who had been trained in germ-free techniques at the Lobund Institute, University of Notre Dame, Indiana, and Milivoj Boranic from Beograde, a trained pathologist, worked with us for several years on gnotobiological approaches to prevention of GvHD. Boranic was the first to attempt a separation of GvHD and graft-versus-leukemia effects in mice. These many activities focused largely on attempts to remove the various obstacles that emerged during the first clinical attempts at bone marrow transplantation.

At the annual meeting of the International Society for Experimental Hematology held in Davis, California in 1971, Mortimer Bortin organized a symposium to commemorate the first two decades of bone marrow transplantation research. The title of the symposium was "Reminiscences: The Past and Thoughts for the Future." The proceedings (4) provide amusing and at times sobering accounts of the very competitive pioneering work of those days. Also some of the forecasting into the next 20 years has been amazingly accurate, as we are now in a position to examine.

1. Crouch BG, VanPutten LM, VanBekkum DW, DeVries MJ. Treatment of total body X-irradiated monkeys with autologous and homologous bone marrow. J Natl Cancer Inst 1961; 27: 53.
2. DeVries MJ, Crouch BG, VanPutten LM, VanBekkum DW. Pathologic changes in irradiated monkeys treated with bone marrow. J Natl Cancer Inst 1961; 27:67.
3. Mathé G, Bernard J, Schwarzenberg L, et al. Essai de traitement de sujects atteints de leucémie aïgue en rémission par irradiation totale suivie de transfusion de moelle osseuse homologue. Rev Fr Etudes Clin Biol 1959; 4: 675.
4. Experimental Hematology. Contributions by Uphoff D, Jacobson LO, Ferrebee JW, et al. 1972; 22: 2.

With Rem Petrov in Moscow, 1968.

Waving participants goodbye and happy return after meeting at Rijswijk, 1970.



Panel discussion on the future of bone marrow transplantation at the annual meeting of the International Society for Experimental Hematology at Davis, California, 1971. (Left to right) George Mathé, Dirk van Bekkum, George Santos, Don Thomas.

Healing Power of Cmomc

George Mathé came to Rijswijk to learn from our mice
How to transplant leukemics. It was no surprise
That the Snag proved to be
An unsurmountable GvHD.
So, the concept of stem cells pluripotential
For the treatment of SCID became rather essential.
DeVries killed the dogma defended by Good
That a thymic defect was its pathological root,
And in view of no T cells nor B cells detected
It must be the stem cell that is badly affected.
It followed that SCID patients should receive
Bone marrow stem cells for complete relief.
Well, that's how it happened that stem cell concentrations
Were used for the first time in clinical transplantations.
With T cell removed there was no need for postponing
This treatment at Leyden, said Leo Jan Dooren and DeKoning.

George Mathé in Paris was among the first to experiment on leukemic mice with total body irradiation and bone marrow transplantation. George had heard of similar work carried out by Marco de Vries in our laboratory and decided to spend a few months during the summer of 1956 in Rijswijk. Shortly afterwards, in 1957, the Vinca accident victims were grafted by Mathé's team and we visited Paris several times to study the progress of the patients. During the next year, Mathé started to treat leukemic children with bone marrow transplantation and found that the secondary syndrome or secondary disease (as GvHD was then called) was the most serious stumbling block. Disputes concerning the cause of secondary disease had been going on since this complication was first reported in mice in 1954 (1) and were focused on whether it was due to a host-versus-graft or to a graft-versus-host immune reaction. Although most of the evidence was in favor of the latter mechanism by 1959 (2), it was 1964 before it was unequivocally proved by the demonstration of a direct relationship between number of lymphoid cells grafted along with the bone marrow and secondary mortality (3). By the same token, it became clear that removal or inactivation of lymphocytes from the graft before transplantation would mitigate or completely prevent acute GvHD.

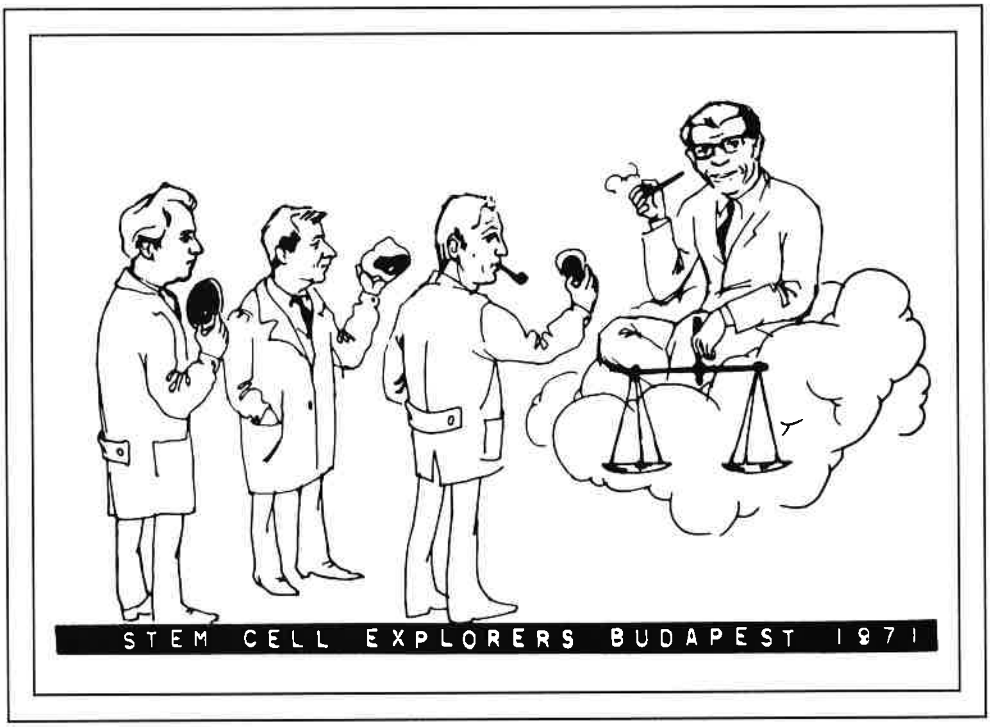
In the meantime, our group had developed an interest in the role of the thymus in GvHD, autoimmune disease, and resistance to infections. Following Jacques Miller's discovery (4) of the key function of the thymus in development of cellular immunity, we became intrigued by the wasting syndrome that he observed after neonatal thymectomy which in some aspects resembled GvHD. We were able to demonstrate the development of autoimmune disease (5). These studies brought us into contact with the pediatricians Dooren and De Koning at Leiden University Hospital. They were treating babies suffering from Swiss Type agammaglobulinemia [later called severe combined immune deficiency, (SCID)], a disease uniformly fatal at that time and thought to be caused by a defect in the development of the thymus. It was treated with grafts of fetal thymus but to no avail, as were many other cellular immune deficiencies. Because of our experience with experimental thymus transplantation, we became involved in clinical transplants and had the opportunity to study these children in great detail. We soon reached the conclusion that the underlying defect of SCID could not be in the thymus, but was more likely to be located in the pluripotential hemopoietic stem cell. Accordingly, we started treating these patients with bone marrow grafts, using lymphocyte poor stem cell concentrates (6). The reason for this precaution was that there had been several reports of fatal GvHD in SCID patients following the transfusion of less than 100 ml of blood.

The first patient did not survive, but in 1968 we were successful (7), and this patient is still fully reconstituted and in excellent health. At that time, Bob Good in Minneapolis was one of the leaders in the field of immune deficiency diseases. Although at first Bob did not accept our views on SCID being a stem cell defect, he nonetheless decided to give marrow transplantation a try and also in 1968 achieved immunological reconstitution following administration of bone marrow and peripheral blood leukocytes (8). These were highly exciting times with fierce competition on both sides of the Atlantic; yet a perfectly open exchange of information and ideas and a lot of mutual respect and friendship.

Karel Dicke and I had developed the so-called purification of stem cells by centrifugation over a discontinuous albumen gradient (9). Karel and I then traveled all over the world to apply this stem cell purification to the treatment of SCID patients (10), but the results with mismatched grafts were not satisfactory. We later learned that in those cases, we were not removing enough lymphocytes. However, a high proportion of permanent cures was obtained with grafts of HLA-identical marrow, so that bone marrow transplantation became established as the only treatment for this disease. T-cell depletion methods have been refined over the years and it is gratifying to note that the results obtained during the past 10 years with T-cell depleted mismatched bone marrow in SCID patients are equivalent to those with matched marrow (11).

1. Barnes DWH, Loutit JF. Spleen protection: the cellular hypothesis. In: Bacq ZM Radiobiology Symposium Liège 1954. London, Butterworths, 1955; 134.
2. VanBekkum DW, Vos O, Weyzen WWH. The pathogenesis of the secondary disease after foreign bone marrow transplantation in X-irradiated mice. J Natl Cancer Inst 1959; 23:75.
3. VanBekkum DW. The selective elimination of immunological competent cells from bone marrow and lymphatic cell mixtures. I. Effect of storage at 4°C. Transplantation 1964; 2:393.
4. Miller JFAP. Three decades of T-ology. Thymus 1990; 16:131.
5. DeVries MJ, VanPutten LM, Balner H, VanBekkum DW. Lésions suggérant une réactivité chez des souris atteintes de la "Runt disease" apres thymectomie néonatale. Rev Fr 1964; 9:381.
6. Dooren LJ, DeVries MJ, VanBekkum DW, et al. Sex-linked thymic epithelial hypoplasia in two siblings. Attempt at treatment by transplantation with fetal thymus and adult bone marrow. J Pediatr 1968; 72:51.
7. DeKoning J, Dooren LJ, VanBekkum DW, et al. Transplantation of bone marrow cells and fetal thymus in an infant with lymphopenic immunological deficiency. Lancet 1969; 1:1223.

8. Gatti RA, Meuwissen HJ, Allen HD, et al. Immunological reconstitution of sex-linked lymphopenic immunological deficiency. Lancet 1968; 1366.
9. Dicke KA, VanHooft JIM, VanBekkum DW. The selective elimination of immunologically competent cells from bone marrow and lymphatic cell mixtures. II. Mouse spleen cell fractionation on a discontinuous albumin gradient. Transplantation 1968; 6:562.
10. VanBekkum DW. Use and abuse of hemopoietic cell grafts in immune deficiency disease. In: Möller G. Ed: Transplant Review 9, 1972, Copenhagen, Munksgaard, 1972.
11. Fischer A, Friedrich W, Levinsky R, et al. Bone marrow transplantation for immunodeficiencies and osteopetrosis: European Survey 1986-1985. Lancet 1986; 8:1080.



Artistic impression by Kelemen of the competing propositions concerning the morphology of the hemopoietic stem cell. (Left to right) Kelemen, Fliedner, van Bekkum, Lajtha. Meeting of Hungarian Hematological Society, Budapest, 1971.

Cmomc Is Born

Joop vanHooft and Karel Dicke
Used albumin bovine sticky;
Gradients based on density
Were spun at low intensity.
And behold! the upper regions
Of the gradients held the legions
Of stem cells nicely T depleted
So GvH could be defeated.
With the stem cells purified to some degree,
the F factor was determined by Lahiri
So that we could make an approximation
Of the real stem cell concentration.
And to settle who was right
We played ping pong through the night.
On that basis the morphological appearance
Of the stem cell was revealed by inference.
With the help of Dicke, Maat and VanNoord
The Cmomc was jointly pulled aboard
At last, to abolish Ted Fliedner's idea
that it was one of the lymphoid family.

With the finding that the distribution of stem cells over a discontinuous density gradient was different from that of more mature cells, the way was open to attempt its purification and identification. About the same time, Ken Shortman in Melbourne was experimenting with continuous density gradients, and R.F. Miller in Toronto was working with velocity sedimentation.

Interest in these new techniques was so strong among both bone marrow transplanters and hematologists that we were able to organize an international workshop on the separation of hemopoietic cell suspensions in 1970 (1). The different methods were demonstrated in the laboratory and the results were compared. The next year we had the first symposium on in vitro culture of hemopoietic cells, another rapidly developing new procedure (2).

The in vitro cloning methods of bone marrow cells as originally introduced by Ray Bradley and Don Metcalf in Melbourne (3), and Dov Pluznik at the Weissmann Institute in Israel (4), and adapted to human marrow by Bill Robinson (5), were contributing increasingly to the quantitative analysis of the hemopoietic system. The various techniques were very much in a pioneering stage and the workshop was used to demonstrate and compare the very divergent methods. With all these new possibilities and an electron microscope facility at Rijswijk, we began looking for cells with specific morphological characteristics in stem cell concentrates.

In 1971 we published a detailed description of the hemopoietic stem cells (Cmomcs) and put an end to the longstanding misconception that the stem cell was a lymphoid cell (6). This distinction was particularly important for bone marrow transplantation, as we recommended removal of the lymphocytes (as the principal inducers of GvHD) and the retention of the stem cells (as essential for repopulation). Following this description, the shape and structure of hemopoietic stem cells became the subject of lively debates among our group and those of Lajtha in Manchester, Fliedner in Ulm, and Kelemen in Budapest. In later years, an increasing number of monoclonal antibodies and lectins were found to be useful in dissecting the various steps in hemopoietic differentiation.

1. VanBekkum DW, Dicke KA, Eds. The separation of haemopoietic cell suspensions. The proceedings of a workshop on the separation of haemopoietic cell suspensions. The Radiobiological Institute TNO, The Netherlands, 1970.
2. VanBekkum DW, Dicke KA, Eds. In vitro culture of hemopoietic cells. The proceedings of a workshop/symposium on in vitro culture of hemopoietic cells. The Radiobiological Institute TNO, The Netherlands, 1971.
3. Bradley TR, Metcalf D. The growth of mouse bone marrow cells in vitro. Aust J Exp Biol Med Sci 1966; 44:287.
4. Pluznik DH, Sachs L. The cloning of normal "mast" cells in tissue culture. J Cell Comp Physiol 1965; 66:319.
5. Robinson WA, Stanley ER, Metcalf D. Stimulation of bone marrow colony growth in vitro by human urine. Blood 1969; 33:396.
6. VanBekkum DW, VanNoord MJ, Maat B, Dicke KA. Attempts at identification of hemopoietic stem cell in mouse. Blood 1971; 38:547.

Presenting the famous bottle of "jonge jenever" to Don Metcalf in 1971. Karel Dicke is in the background on the left.

With Dov Pluznik on ship, 1972.

With Bill Robinson (left) and Don Metcalf at the Second International Workshop on Hemopoiesis in Culture, Arlie House, Virginia, USA, in 1973.

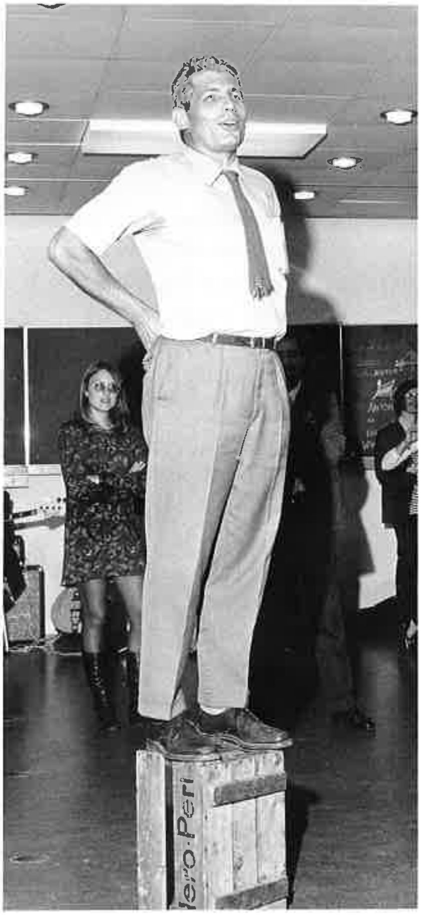
Cmomc Needs Help

Yet its clinical applications
Provided many complications.
In primates the gradient had to be combined
With other measures until much more refined.
Depletion of T cells became part of the setting,
Like monoclonals, lectins and rosetting.
Hans Balner took Jon vanRood's leukocyte matching
To monkeys, to help us with donor catching.
He also provided some ALG
That had been tested--for an attractive fee.
Nicole Muller-Berat studied immunosuppression,
Her genever regimen made quite an impression.
Van derWaaij became famous by his insistence
That the key to success lies in colonization resistance.
With Hendriks and Heidt he used laminar flow
To reverse isolation and for Vossen to show
That decontamination, complete and selective
Reduced GvHD also effective.
Yes, every Cmomc instillation
Was collected by Bortin for his IBMT Registration.

This part of the Ballad refers to the period of preclinical work with T-cell depleted stem cell concentrates in the monkey model of acute GvHD. Although our depletion was only about 90 percent, it was quite effective in doubling the survival time of the animals, but it was not yet good enough to prevent mortality from GvHD in mismatched unrelated monkeys. Nicole Muller-Berat, now the Chief Editor of *Leukemia*, joined our monkey clinic and helped us combine stem cell purification with pre- and posttransplant ALG, cyclophosphamide, and other immune suppressive agents. The modalities of decontamination and isolation were added by the bacteriologist Dick van der Waay, later succeeded by Peter Heidt. We were able to study bone marrow grafting in germ-free and decontaminated mice and in decontaminated monkeys and dogs. This technique was effective in mitigating GvHD, and decontamination with barrier nursing in laminar flow units was introduced successfully in the clinic by Jaques Vossen, who joined the pediatric bone marrow transplant group at Leiden (1).

Also, from 1965 the progress made in HLA typing allowed application of this principle in bone marrow transplantation. Typing the rhesus colony allowed us to compare various matches. This resulted in the important conclusion that prevention of GvHD in MHC-identical siblings required between one and two log depletion of T lymphocytes, but to get the same results in mismatched unrelated combinations, between three and four log had to be removed or inactivated, which proved to be difficult (2). Apart from our results with immune deficiencies in Leiden, Prentice in London (3) was the first to convincingly demonstrate the value of T-cell depletion in adult patients.

Bob Löwenberg, Ton Hagenbeek, and Karel Dicke all spent several years in research at the laboratory in Rijswijk before they completed their clinical training as hematologists. They wished to start their own bone marrow transplant operation in Rotterdam, which unfortunately, took longer than expected. Karel could not wait and left to start his successful autologous bone marrow transplant program at M.D. Anderson Cancer Center in Houston and he is considered the founder of ABMT in the United States. It was 1980 before bone marrow transplantation could be started at the Cancer Hospital in Rotterdam. The first accomplishment was the application of the T-cell depletion method, which led to a complete confirmation of the monkey data (4). The routine use of T-cell depletion has made GvHD (in HLA-identical combinations) practically non-existent. At the same time it greatly reduced the incidence of interstitial pneumonitis. It has transformed the bone marrow transplantation ward by drastically reducing the high incidence of complications. As is not uncommon in medicine, it took almost two decades between the basic discovery of the principle of T-cell depletion as an effective means of preventing GvHD and its full implementation in the clinic. Most of the delay was caused by difficulties in developing techniques for removing T-lymphocytes to below one percent.



Thanking participants at a party, 1971.

1. Vossen JM, Heidt, PJ, Guiot HFL, Dooren LJ. Prevention of acute graft versus host disease in clinical bone marrow transplantation: Complete versus selective intestinal decontamination. In: Sasake S, Ozawa A, Hashimoto K, Eds. Recent Advances in Germfree Research, Proceedings of the 7th International Symposium in Gnotobiology. Tokai University Press, Tokyo, 1981; 573.
2. Wagemaker G, Heidt PJ, Merchav S, VanBekkum DW. Abrogation of histocompatibility barriers to bone marrow transplantation in rhesus monkey. In: Baum JS, Ledney GD, Thierfelder S Eds. Experimental Hematology Today 1982. S. Karger, Basel, 1982; 111.
3. Prentice HG, Blacklock HA, Janossy G, et al. Depletion of T lymphocytes in donor marrow prevents significant graft-versus-host disease in matched allogeneic leukaemic marrow transplant recipients. Lancet 1984; 1:472.
4. Löwenberg B, Wagemaker G, VanBekkum DW, et al. Graft-versus-host disease following transplantation of "one log" versus "two log" T-lymphocyte-depleted bone marrow from HLA-identical donors. Bone Marrow Transplant 1986; 1:133.

Selling apple trees during drive for cancer center in Rotterdam, 1977.

Table speech at yet another meeting.

Cmomc Rides Alone

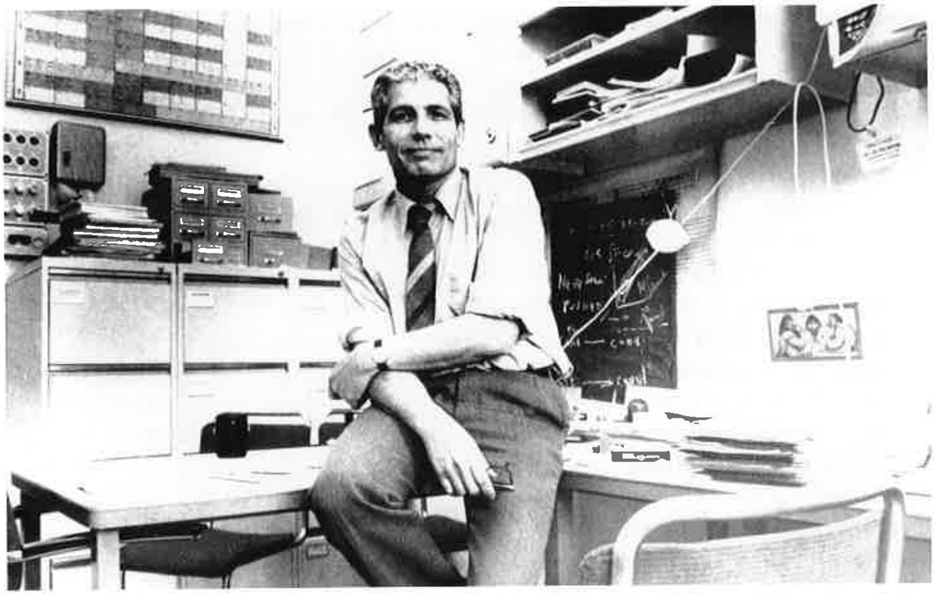
Alas, it was soon found that T cell resection
Increased the percentage of transplant rejection.
More preclinical work with monkeys and dogs
Reduced the host's T cells with several logs.
Here we saw Huibert M. Vriesendorp
Always in competition with Reiner Storb.
The expected result was higher dose irradiation
Which had to be given by fractionation.
This was also the way of conditioning
By Richard O'Reilly at Sloan Kettering
To get excellent takes so he emphasized
With the bone marrow grafts being Reisnerized.

Riding alone refers to grafting of stem cells without lymphocytes. This proved to be more difficult than foreseen because the GvHD reaction itself had an immunosuppressive effect and this added to the conditioning (1). Our early clinical attempts with purified stem cells were in SCID patients and with relatively small numbers of cells because we were afraid to induce GvHD and were not concerned about take failure in these totally immune-deficient children. As early as 1970, Dicke and I reported that we had to increase the dose of TBI from 7.7 Gy to 8.5 Gy to assure near 100 percent takes in monkeys when using lymphocyte-depleted stem cells (2). At that time we were achieving only one log depletion and were grafting unrelated mismatched monkeys. Later we went to three log or more depletion and observed that the irradiation dose had to be increased still further. This important issue was worked out between 1977 and 1983, mainly by Gerard Wagemaker in monkeys (3) and Huib Vriesendorp, et al (4) in dogs. It turned out that highly T-cell depleted stem cells always require more conditioning than unmodified bone marrow, but the increase, in terms of radiation dose, is less in the case of MHC-identical sibling combinations than in mismatched unrelated transplants.

On the basis of these results, the clinical regimen in Rotterdam was established at two fractions of five Gy in combination with cyclophospamide and ara-C for leukemics and it resulted in 100 percent takes. At about the same time, Burnet, et al, showed that his high take failure rate could be prevented by increasing the radiation dose by about two Gy (one fraction in case of fractionated radiation) (5). In 1976, Yair Reisner studied our stem cell separation techniques in Rijswijk and went on to modify the method by adding lectin agglutination. That method was subsequently tested in monkeys and successfully introduced in O'Reilly's transplant unit in New York (6).

When more clinical groups began to use T-cell depleted bone marrow in the treatment of leukemia, it was noted by some that the relapse rate rose higher than it had been previously with unmodified bone marrow. From comparative studies in the BNML rat model of acute leukemia, Hagenbeek and his associates calculated that the graft-versus-leukemia reaction was not very significant in terms of log leukemic cell kill and that a moderate increase in conditioning regimen, probably similar to that needed to prevent take failures, was predicted to solve this problem (7). Those groups that intensified their conditioning regimen have not, indeed, seen higher relapse rates. The latest report from Martelli in Perugia seems to support this concept, even in the case of chronic myeloid leukemia, which was particularly relapse prone following the switch to T-cell depletion (8).

1. Vriesendorp HM. Engraftment of hemopoietic cells. Bone Marrow Transplant 1985; 2;73.
2. Dicke KA, VanBekkum DW. Avoidance of acute secondary disease by purification of hematopoietic stem cells with density gradient centrifugation. Exp Hematol 1970; 20:126.
3. Wagemaker G, Heidt PJ, Merchav S, VanBekkum DW. Abrogation of histocompatibility barriers to bone marrow transplantation in rhesus monkeys. In: Baum JS, Ledney GD, Thierfelder S, Eds. Experimental Hematology Today 1982. S. Karger, Basel. 1982; 111.
4. Walma EP, Vriesendorp HM, Zurcher C, VanBekkum DW. Engraftment of stem-cell-enriched bone marrow fractions in MHC-identical dogs after fractionated total-body irradiation. Transplantation 1987; 43:818.
5. Burnet AK, Hann IM, Rogertson AG, et al. Prevention of graft-versus-host disease by ex vivo T-cell depletion: Reduction in graft failure with augmented total body irradiation. Leukemia 1988; 2:300.
6. Reisner Y, Kapoor N, Kirkpatrick D, et al. Transplantation for severe combined immunodeficiency with HLA-A,B,C,DR incompatible parental marrow cells fractionated by soybean agglutinin and sheep red blood cells. Blood 1983; 61:391.
7. Hagenbeek A, Martens ACM, Schultz FW, VanBekkum DW. Cure after allogenic bone marrow transplantation: chemo-radiotherapy and/or graft-versus-leukemia? Bone Marrow Transplant 1990; 6:91.
8. Aversa F, Pelicci PG, Terenzi A, et al. Results of T-depleted BMT in chronic myelogenous leukaemia after a conditioning regimen that included thiotepa. In: Abstracts; 17th Annual Meeting of the EBMT, 1991; 12.



Dirk van Bekkum in his lab, 1976.

Cmomc's Future

That T lymphocytes not enhance reconstitution
Was recently Gerritsen's contribution,
But suppressor cells may be the ones that are grooming
The Cmomc, at least that's what Shosh Knaan is assuming.
And Wielenga in his thesis defended
That bone marrow grafting not be recommended
Following overexposure to radiations
So that we can focus on new indications.
Lysosomal diseases, the mouse called Twitcher
Made Hoogerbrugge one degree richer
And autoimmunity, such as arthritis,
Diabetes and allergic encephalitis,
But not to forget what Valerio teaches
That stem cell gene therapy within reach is.

This part refers to the investigations of Wieland Gerritsen (1), who showed that T lymphocytes in the bone marrow graft of monkeys do not perform a trophic function: the rate of repopulation of hemopoiesis was not changed by T-cell depletion of autologous bone marrow grafts. It also refers to interaction between suppressor cells and proliferating stem cells as postulated by Shoshan Knaan and to the interesting observations of Jelle Wielenga that if sufficient supportive care is provided, rhesus monkeys can now survive unexpectedly high doses of total body irradiation, bordering on the dose that induces mortality from gastrointestinal damage (2). These results of course are very interesting in the development of treatment strategies for radiation accident victims.

The second part of this poem points to the many exciting new applications for marrow grafting that are being developed both in the laboratory and in the clinic: the treatment of hereditary lysosomal enzyme diseases with bone marrow transplantation that required an insight into the ability of macrophages and other white cells to penetrate the brain in sufficiently large numbers to allow normalization of the enzyme levels. Such studies were undertaken in the galactosyl ceramidase deficient ("Twitcher") mouse by Peter Hoogerbrugge (3), who earned his PhD degree by doing this research; Ikehara's (4) and my own attempts to treat experimental autoimmune diseases with bone marrow replacement (5); and the work started by Dinko Valerio some years ago in our laboratory under the heading of somatic cell gene therapy in ADA deficiency. This research profits greatly from the abundant availability of culture and isolation techniques for hemopoietic stem cells and of in vivo models. In my lecture on "Methodology Apropos Futurology" during the bone marrow transplantation meeting at Davis in 1971, I said, "I would like to think of intracellular engineering in contrast to cellular engineering." It is nice to live to see your dreams come true, but I was too optimistic in my next statement in the same talk; "We can well expect the application of intracellular engineering (in relation to hemopoietic cells) in the near future" (7).

1. Gerritsen WR, Wagemaker G, Jonker M, et al. The repopulation capacity of bone marrow grafts following pretreatment with monoclonal antibodies against T lymphocytes in rhesus monkeys. Transplantation 1988; 2:301.
2. VanBekkum DW, Wielenga JJ, VanGils F, Wagemaker G. Factors influencing reconstitution by bone marrow transplantation. In: Dainiak N, Cronkite EP, McCaffrey R, Shadduck RK Eds. The Biology of Hematopoiesis. 1990; 479.
3. Hoogerbrugge PM, Suzuki Ki, Suzuki Ku, et al. Donor-derived cells in the central nervous system of twitcher mice after bone marrow transplantation. Science 1988; 239, 4843:1035.
4. Ikehara S, Kawamura M, Takao F, et al. Organ-specific and systemic autoimmune disease originate from defects in hemopoietic stem cells. Proc Natl Acad Sci 1990; 87:8341.
5. VanBeusechem VW, Kukler A, Einerhand MPW, et al. Expression of human adenosine deaminase in mice transplanted with hemopoietic stem cells infected with amphotropic retroviruses. J Exp Med 1990; 172:729.
6. VanBekkum DW, Bohre EPM, Houben PFJ, Knaan-Schanzer S. Regression of adjuvant-induced arthritis in rats following bone barrow transplantation. Proc Natl Acad Sci USA 1989; 86:10,090.
7. Experimental Hematology. Contributions by Uphoff D, Jacobson LO, Ferrebee JW, et al. 1972; 22: 2.

Bone marrow transplant team visiting a member at the hospital. In bed Shoshan Knaan, expecting a baby, 1976.

Payoff at institute party with Hans Balner (center), Director of the Primate Center, 1980.

Play acting at a party with Map van Es (left), Director of the Primate Center, 1985.

Cmomc Replicated and Frozen

Another break-through was the introduction
Of methods for in vitro colony production
By Pluznik and Sachs and by Bradley and Metcalf.
(The order of names is merely on behalf
Of the rhyming, I assure the reader.)
It was Dicke who followed with fetal cell feeder
And with Löwenberg thought up many a trick
That allowed us to study what makes stem cell tick.
Through liquid cultures a new horizon
Was revealed to us all by Jim Eliason.
The first clumsy ventures were made to capture
The mysterious colony stimulating factor
As produced by leukocytes, fibroblasts murine,
Pregnant uterus or leukemics urine
Soon to be replaced by Stem Cell Activating Factor
Which made Wagemaker our biggest contractor.
Now he says it is Interleukin 3
And that we are all millionaires to be.

Nakeff came to focus on the formation
Of megakaryocytes and their relation
To the stem cell. Ulrich Schaefer
Used the assay to develop safer
Methods of cryopreservation
Of stem cells for later transplantation.

This relates the line of research that dealt with in vitro culturing of hemopoietic cells on feeder layers and in a conditioned medium. The pioneers in that field were already mentioned in "Cmomc is Born." The dream of all transplanters was to grow as many pluripotent stem cells in flasks as needed for transplanting patients, in the process getting rid of undesirable cell types such as T lymphoycytes and leukemic cells. The first experiments with supernatants containing hemopoietic growth factors were performed by Bob Löwenberg and Karel Dicke in the early seventies. Gerard Wagemaker finally purified and cloned his stem cell activating factor (SAF), which turned out to be IL-3 (1).

Ulrich Schaefer worked with us in 1970 and 1971. With clonogenic culture methods and the monkey model he perfected the cryopreservation of stem cells, which has become so useful in autologous bone marrow grafting (2). He then went back to Essen, where he is running one of the largest bone marrow transplant units in Germany.

1. Wagemaker G, Burger H, VanGils FCJM, et al. Interleukin-3. Biotherapy 1990; 2:337.
2. Schaefer UW. Preservation of bone marrow for transplantation. In: VanBekkum DW, Löwenberg B, Eds. Bone Marrow Transplantation 11, 1985; 513.

Entertaining at the Eighth Annual Meeting of the International Society for Experimental Hematology at Rotterdam with Peter Heidt (accordian) and Ger van den Engh (guitar), 1979.

"The Saints Are Sailing In" being played during party on the lake at Rotterdam at the Eighth Annual Meeting of the International Society for Experimental Hematology, with Ger van den Engh (guitar) and Ton Hagenbeek (singer) just behind trumpet player.

The Children of Cmomc

The density gradients and CFU in combination
Made the scene for the study of cell differentiation.
Ger vandenEngh set the pace for dissection
Of cellular hierarchy and all its connections
With Simon Bol, Neil Williams and Hether
They tried to put the pedigree together.
Hurrah! to density, size, charge and colony formation
Could now be added yet another separation
Provided by the FACS. Its laser beams and electronics
Brought in a generation of neurotics.
The building of machines became obsession
Computers were their only dear possession.
The RELACS 2 was built, to be succeeded
By RELACS 3, even more badly needed
For analyzing chromosomes in flow
And to prevent our budgets falling low.
A new machine for sorting algea
Was named OPA out of nostalgia.
Jan Visser, Bauman, Ger and Barbara
Were joined by Baines, Dries Mulder and Castagnola,
Dubelaar, Richard Jonker and Herweijer,
Willem Stokdijk, Peter deVries and Jan Bayer.
And VanDekken, whose name means confusion,
Used ISH for his nuclear allusion.
The stem cell became purer and purer,
But from Stanford rose an even better conjurer
Who showed us the end of the road. Came Mike Dexter
To rescue with his relative enrichment factor.

In 1975 we received a large program grant from the Organization for Fundamental Research to pursue the study of the hemopoietic stem cell and its derivatives. It allowed us to expand the stem cell group with no less than 10 people for a period of five years and to develop the technique of light-activating cell sorting that was emerging at that time. This research line was aimed at the development of new techniques for distinguishing between the successive steps in the differentiation along the various pathways, to define the conditions and factors for proliferation and differentiation, and to characterize the line-specific precursor cells. The motors of the program were Ger van den Engh and Gerard Wagemaker, and it was carried out in collaboration with Otto Vos' group at the Erasmus University at Rotterdam. These years were among the best of my entire research life because of the freedom allowed us to pursue our own ideas and the many visiting scientists attracted, among them Don Metcalf in 1981.

The first prototype cell sorter to become operational in the Netherlands was part of the instrumentation for this program. It was soon found to be insufficient for the ambitious initiators of this development. Van den Engh, Visser, and Stokdijk started the construction of the Rijswijk electronic light-activated cell sorter with two laser sources (RELACS 2). A few years later, inspired by developments in Livermore, California, a three laser machine (RELACS 3) was constructed that permitted the sorting of chromosomes. Our institute became the center of cell-sorting techniques and it evoked an enormous amount of collaboration with scientists from all over the world.

The purification of stem cells was gradually improved (1). In 1984, Jan Visser and Jan Bauman achieved a 100- to 200-fold enrichment of the most primitive stem cells by a combination of density centrifugation, fluorescent wheat germ agglutin conjugates, and anti-H2 K antibody (2). Later, Weissman's group at Stanford claimed a 10-fold higher purification (3). Quite a discussion about the validity of these claims followed, with Mike Dexter from Manchester pointing out that we were probably all getting similar degrees of maximal enrichment (4). More recently in situ hybridization (ISH) techniques have been developed in our laboratory both for microscopic and for in-Flow purposes (5).

1. Visser JWM, VanBekkum DW. Purification of pluripotent hemopoietic stem cells: Past and present. Exp Hematol 1990; 18:248.
2. Visser JWM, Bauman JGJ, Mulder AH, et al. Isolation of murine pluripotent hemopoietic stem cells. J Exp Med 1984; 59:1576.
3. Spangrude GJ, Heimfeld S, Weissman IL. Purification and characterization of mouse hematopoietic stem cells. Science 1988; 241:58.
4. Dexter TM, Lord BI. Reply to letter by Weissman et al. Immunol Today 1989; 10:6.
5. Bauman JGJ, VanDekken H. Flow cytometry of fluorescent in situ hybridization to detect specific RNA and DNA sequences. Acta Histochem (Suppl) 1989; 38:65.

Presenting the Golden Stem Cell plaque to Leo Jan Dooren (middle) and Jacques Vossen (left) on occasion of the 100th pediatric bone marrow transplant at their ward in Leiden, 1988.

Cmomc Goes Viral

The stem cell was subject to viral infection.
Emiel Brommer took Rauscher under Bentvelzen's direction
To study the graft of erythroblastosis
With Nooter to show that the virus imposes
Itself onto Cmomc. But Hasthorpe denying.
Dov Zipori invented a fibroblast line
That was feeding the stem cells just as well
As Manchester's famous adherent cell.
The first primitive gene therapy was conducted
By Shoshan Merchav who has reconstructed
The stem cells of W/W vee
With the Rauscher to help them make spleen colony.
It is mighty exciting to try transplantation
With marrow, for treating AIDS patients,
But first we should know if Cmomc gets away
From the virus discovered by Luc Montagnier.

Retroviruses have been the subject of research at the Radiobiological Institute since Peter Bentvelzen joined us in 1969 to strengthen our program on radiation carcinogenesis. We thought that his knowledge of genetics and oncogenic viruses was essential for a comprehensive approach to malignant transformation.

In view of the large number of people with an interest in hemopoiesis and leukemia, it was unavoidable that the primary target for the virological studies was to be the hemopoietic stem cell. The finding that infection of W/W v bone marrow cells with the Rauscher virus restores the ability to form macroscopic spleen colonies to these cells, was considered the first primitive example of gene therapy with the use of a retrovirus vector (1).

During the past few years the retrovirologists in our institute have been concentrating their efforts on the HIV problem for obvious reasons: our institute has long-standing experience with all kinds of immunosuppressions, we have the largest chimpanzee colony in Europe, and the AIDS epidemic needs all available workers. Once again, part of the effort has focused on the hemopoietic stem cells, in particular to unravel which cells are infected by the virus (2). If the preliminary finding that the hemopoietic stem cell remains uninfected can be confirmed, autologous bone marrow transplantation with stem cell concentrates will become a serious treatment consideration.

1. Merchav S, Wagemaker G, Van-Bekkum DW. Reconstitution of the W/W v stem cell differentiation defect by infection with Rauscher leukemia virus. J Natl Cancer Inst 1985; 75:361.
2. Slachmuylders JFAM, Wagemaker F, Visser TP, et al. Bone marrow progenitor cells in SIV infected rhesus monkeys remain uninfected despite hematologic abnormalities in AIDS. Proceedings of 8th Annual Symposium on Nonhuman Primate Models for AIDS, 1990.

Play acting at New Years party, 1988. Dirk van Bekkum with Ton Hagenbeek in referee seat at right and surrounded by chorus girls.

Real ballad singing at party following Panorama Stem Cell Symposium. (Left to right) The Victim, Ger van den Engh, Ton Hagenbeek, Karel Dicke, and Richard O'Reilly, 1990.

Purging of Cmomc

The story of Cmomc cannot be completed
Before he has all his bad brethren defeated.
Leukemia research began to go well
After we discovered the BNML.
It was Ormai who tried its extermination,
With extracorporeal irradiation
He made Hagenbeek running the samples of blood
To the X-ray machine and back to the rat.
Our polymethacrylic acid
Was fabulous, you could have guessed it
Leukemic cells were mobilized, so Bill Ross wrote,
It also put an end to Cronkite's favored goat.
Then came the episode of cellular kinetics
With Massimo Aglietta improving his athletics.
At tennis, his reactions mainly vocals
Have greatly entertained the locals.
With nocturnal schemes of dosing
Il Dottore kept proposing
That he could efficiently
Cure with chemotherapy.
Sonneveld and Louisa Colly
Tested numerous protocolli.
Prins found Cmomc to be replaced
From the marrow they were chased,
But upon complete remission
Could resume the competition.
Minimum residual disease, according to Ton,
Has been going on and on.
It explains Dr. Martens' intensive researches
To develop the most devilish purges
As well as Freriks' and Schultz' calculations
From mathematical simulations.

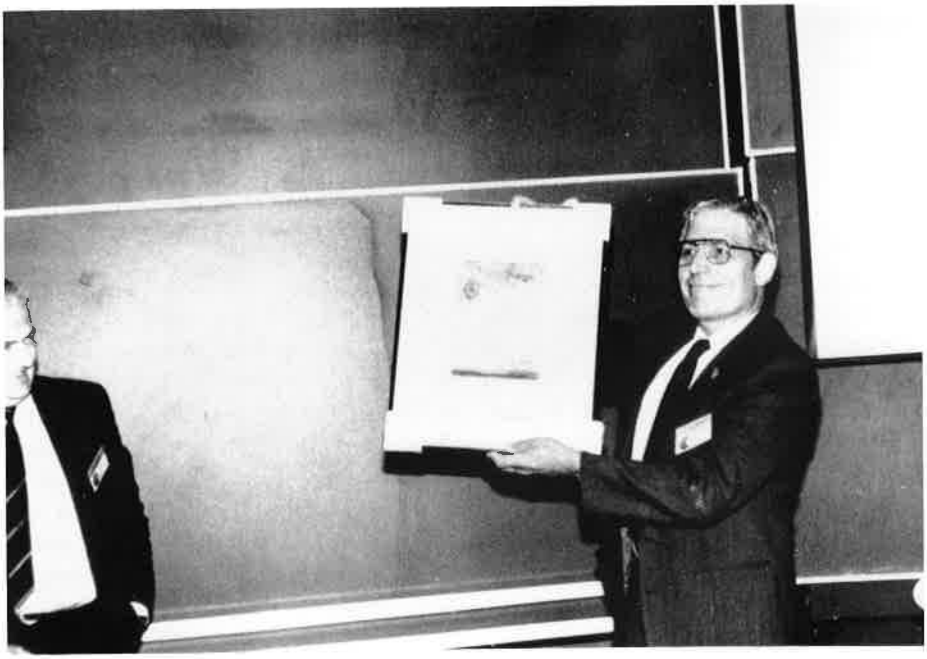
There is hope for the future as long as we smell
In the labs and the corridors our BNML.

This rather lengthy narrative refers to our research efforts in leukemia. This has always been an integral part of our experimental hematology program. In the early days of bone marrow transplantation, Marco de Vries used a transplantable lymphosarcoma in C57BL mice to explore the differences in therapeutic results between allogeneic and autologous bone marrow transplantation (1). This model was also employed in the beginning of our experiments with extracorporeal irradiation of the blood (ECIB), to be replaced by the promyelocytic leukemia in the Brown Norway rat (the BNML). To improve the results of ECIB, it seemed attractive to mobilize the leukemic blast cells from the tissues into the peripheral blood (2). These investigations led to a close collaboration with the groups of Gene Cronkite, Ted Fliedner, and the late Sven Killmann.

The BNML model was fully explored by Ton Hagenbeek who has used it since for a variety of fruitful investigations on many other aspects of leukemia. The BNML has been exceptionally useful because of its predictive value for human leukemia. It has been adopted by at least 20 laboratories all over the world. The term "minimal residual disease," as introduced by Ton Hagenbeek, has become a key term in our thinking on the treatment of leukemia (3).

One of the most important and controversial issues was the treatment of leukemia with autologous bone marrow transplants. Purging of leukemic cells, seemingly a condition sine qua non, was shown to be less important according to quantitative analysis in the BNML model. Instead, it is the eradication of residual leukemic cells by the conditioning that determines the outcome of the treatment. It is gratifying to observe that careful clinical studies of the past years tend to confirm these experimental findings.

1. DeVries MJ, Vos O. Treatment of mouse lymphosarcoma by total-body X-irradiation and by injection of bone marrow and lymph node cells. J Natl Cancer Inst 1958; 21:1117.
2. Ormai S, Hagenbeek A, Palkovits M, VanBekkum DW. Changes of lymphokinetics in the normal rat, induced by the lymphocyte mobilizing agent polymethacrylic acid. Cell Tissue Kinet 1973; 6:407.
3. Martens ACM, VanBekkum DW, Hagenbeek A. Minimal residual disease in leukemia: Studies in an animal model for acute myelocytic leukemia (BNML). Int J Cell Cloning 1990; 8:27.



Being honored by the International Society on Gnotobiology at tenth meeting in Leiden, 1990.

Cmomc Transcendent

We are now back to zero, the CFU-S
Is a mixture of stem cells, there seems no safe access
To the Cmomc, Ploemacher's cobblestones
Pave the way to the hell, they are breaking our bones.
Lies the answer perhaps in the LTBMC?
Or are we condemned to the MRA?
No, it appears that our only salvation
Will be to rely on long term repopulation.

Through the distance of time after transplantation
We may vaguely distinguish Cmomc's procreation
From chimaera it sprang, to chimaera returned,
Well fellers, let's cast the hounds and continue the hunt.

The end of the ballad alludes to recent suggestions that the purest stem cell preparations ever made are still composed of a number of different cells. Beginning with the separation of CFU-S into rhodamine dull and rhodamine bright subpopulations (1,2), more recently there is a possible distinction between early and late repopulating stem cells (3). In Rotterdam, Rob Ploemacher has been able to separate CFU-S from stem cells with marrow repopulating ability (MRA) and refers to primitive cells in culture on stromal layers as cobblestones (4). LTBMC stands for the long-term bone marrow cultures developed by Dexter's group in Manchester, which have been extremely useful for studying stem cells with repopulating ability in vitro. Because of those recent technical refinements, confusion is taking the place of assurance about the identity of the pluripotent hemopoietic stem cell and there is opportunity for new and even more exciting research.

1. Bertoncello I, Hodgson GS, Bradley TR. Multiparameter analysis of transplantable hemopoietic stem cells. I. The separation and enrichment of stem cells homing to marrow and spleen on the basis of Rhodamine-123 fluorescence. Exp Hematol 1985; 13:999.
2. Mulder AH, Visser JWM. Separation and functional analysis of bone marrow cells separated by Rhodamine 123 fluorescence. Exp Hematol 1987; 15:99.
3. Jones RJ, Wagner JE, Celano P, et al. Separation of pluripotent haematopoietic stem cells from spleen colony-forming cells. Nature 1990; 347:188.
4. Ploemacher RE, Brons HC. Separation of CFU-S from primitive cells responsible for reconstitution of the bone marrow hemopoietic stem cell compartment following irradiation: evidence for a pre-CFU-S cell. Exp Hematol 1989; 17:263.

Farewell lecture at Leiden University, 1990.

Dirk van Bekkum with partners at a favorite sport.

Another favorite sport.

Combining chores with yet another favorite sport.

Relaxing after still another favorite sport.

CURRICULUM VITAE

Dirk Willem Van Bekkum

PERSONAL

Born:	July 30, 1925, Batavia, Indonesia
Marital Status:	A.R.E. Kylstra, 4 daughters

EDUCATION

1950	State University, Leiden, M.D.
1952	State University, Leiden, Ph. D. (Cum Laude)

POSITIONS

1950-52	Research Physician, Department of Endocrinology, University Hospital, Leiden
1952-55	Staff member, Medical Biological Laboratory of the National Defence Research Organization TNO
1955-60	Head, Department of Radiobiology of Medical Biological Laboratory of the National Defence Research Organization TNO
1960-90	Director, Radiobiological Research Institute of the Organization for Health Research TNO, Rijswijk, The Netherlands
1966-90	Professor of Radiobiology, Erasmus University Rotterdam
1967-90	Professor of Experimental Transplantation Biology, State University, Leiden
1984-88	Director for Research, Division of Health Research TNO
1977-	Executive director of the Comprehensive Cancer Center Rotterdam

AWARDS

1948	British Council Scholarship, Biochemistry, Oxford (Prof. R.A. Peters)
1960	Quantannual Award of the "Izaak Korteweg and Anna Ida Overwater Foundation" for Achievements in the Field of Bone Marrow Transplantation, The Netherlands
1973	Elected to Royal Academy of Arts and Sciences, The Netherlands
1975	Fogarty International Scholarship, National Institutes of Health, Bethesda, M.D., United States
1983	The J. van Loghem Award for Immunology, The Netherlands
1985	Bekales Special Award for Achievements in Leukemia Research, Belgium
1986	The 1986 Award of the "Federation of Medical Scientific Societies," The Netherlands
1987	Knighthood, Order of the Lion of the Netherlands
1990	Medal of Merit of the City of Rotterdam

COUNCIL AND ADVISORY COMMITTEE MEMBERSHIPS

1959-67	Secretary Dutch Society for Radiation Biology 1967-70 President
1962-81	Founding Council Member, European Organization for Research on Treatment of Cancer (EORTC) 1969-75 President
1965-74	Council Member, Transplantation Society 1973-74 Vice-President
1966-83	Council Member International Association for Radiation Research (IARR) 1970-74 Secretary-Treasurer 1979-83 President
1969-86	Member Health Council of The Netherlands
1969-	Board Member Foundation "Life Sciences and Society" (Stichting Bio-Wetenschappen en Maatschappij) 1988-91 Presiden
1972-77	Member Board of Directors of the International Society for Experimental Hematology (ISEH) 1975-76 President
1973-76	President of the Advisory Committee of the International Bone Marrow Transplant Registry

PUBLICATIONS

Total: over 400

MAJOR RESEARCH INTERESTS

Radiation biology, transplantation biology, immunology, oncology, experimental bone marrow transplantation, and experimental hematology

A HEART TRANSPLANTATION NARRATIVE: THE EARLIEST YEARS

Eugene Dong and as told by
Norman E. Shumway
and Richard R. Lower

Address: Department of Cardiovascular Surgery
Stanford University School of Medicine
300 Pasteur Drive
Stanford, California 94305

Norman Shumway

Richard Lower

Eugene Dong

A HEART TRANSPLANTATION NARRATIVE: THE EARLIEST YEARS

Eugene Dong and as told by Norman E. Shumway and Richard R. Lower

On a bright winter day in 1959, Eugene Dong, M.D. traveled to Stanford University at Palo Alto, looking for a training position in surgery. He was in the midst of a medical internship in the Columbia division at Bellevue Hospital in New York City. However, both his alma mater, the University of California at San Francisco, and the Columbia surgical service at Bellevue wanted him to take a surgical internship before considering him for a surgical residency. So Dong was trying his luck at a new school and hospital.

The dean of the new Stanford school, Robert Alway, M.D., had told Dong and other inductees at the 1959 Alpha Omega Alpha honor medical society induction dinner to consider Stanford's new direction in medical research at a new facility in Palo Alto.

By 1959, few established surgeons transferred down from Stanford-Lane in San Francisco, which had been a respected, but clinically oriented medical school. Of particular relevance to the advancement of cardiac surgery science was the fact that Frank Gerbode, M.D., a San Francisco pioneer in heart surgery, elected to stay in San Francisco.

The new chairman of surgery was J.G. Allen, M.D., a surgical researcher from the University of Chicago whose academic credentials included editing a textbook of surgery and studies on plasma and hepatitis. On the particular day of Dong's visit, Roy B. Cohn, M.D. was acting department chairman. Cohn was one of the few established Stanford surgeons who made the move. Cohn was later to perform the first kidney transplants on the west coast between identical twins and become the mentor for Samuel Kountz, M.D. Initially Cohn indicated that there were no positions available for Dong. After a bit of conversation, Cohn learned that Cohn and Dong's uncle were poker playing students together at the old Stanford Medical School. Of such trivialities arose Cohn's suggestion to Dong that maybe a young cardiac surgeon named Norman Shumway might be interested in having a research fellow for a while.

Norman Shumway, M.D., Ph.D. was not a man to stand on the formalities either in training or of position. Shumway appeared in an office which was no larger than five feet by 10 with a single window in the far side opening on to the center well of the surgical wing of the medical school. The office was shared with another, and the two desks side by side were standard chrome-trimmed tan metal desks.

After the briefest of interviews with Dong, Shumway indicated he would support Dong's application for a NIH postdoctoral fellowship. In the meantime, Shumway asked Dong if he would like to see an animal in the surgical research laboratory which had just survived a heart transplant operation.

The medical school building was attached to the Palo Alto-Stanford University Hospital. This hospital was as much an experiment in marrying a university medical staff with a community physician staff as was the medical school's marriage with the scientific university community. Although the hospital was subsequently purchased by Stanford and became the Stanford University Hospital, its schizophrenic birth has lingering effects.

The surgical wing was arranged such that the offices were directly across a six-foot hallway from the laboratories. In Shumway's case, his laboratory was just a few doors down the hall. The laboratory was 30 by 30 feet in size. There were freshly constructed operating tables, surgical lights, an electrocardiographic machine, and a bulky heart lung machine using the latest technology: a Kay-Cross rotating disk oxygenator. And there was indeed a frisky dog with a recent surgical scar. Also present was the surgical resident, Richard Lower, M.D., who had operated on this the first animal to receive a heart from another animal in the "orthotopic" position and live. It is fair to say that among the three present that day, Shumway, Lower, and Dong, none realized the long-lasting relationship they all would have with the field of heart transplantation and with each other.

There was brief but extensive media coverage after Cohn mentioned the accomplishment on a San Francisco television station reviewing the year's medical news. In the print media, Lower characterized the transplantation as a 'technical stunt,' recognizing the significant immunological barriers still to be overcome. The media exposure brought unwelcome threats to Lower from the fringes of society. He would later be brought to trial by the State of Virginia for a donor's death which was successfully defended against. But, to paraphrase George Bernard Shaw, today's heresies are tomorrow's truths.

Lower, like Dong, arrived at Stanford because Lower had strayed off the beaten path for surgical training. Lower was raised in Michigan and went to medical school at Cornell. An interest in the outdoors caused him to choose the University of Washington in the northwest for his surgical residency in 1956. However, during his internship, Lower broached the subject of a shorter training period with the chairman, Dwight Harkins, M.D., because of Lower's initial interest in becoming a general practitioner. Harkins' inflexibility lead Lower to Stanford-Lane Hospital in San Francisco. The surgeon in charge of residency training there, Victor Richards, M.D., indicated that he could care less how long it took Lower to achieve the training he wanted.

At that time, Stanford required their surgical residents to spend some time in research. The physical facilities of the Stanford surgical laboratories were relics of a past era even for the 1950s. A single large laboratory was used both for research and for a dog surgery course for fourth-year medical students. The wash basins were made of cement. The plumbing was exposed. There were smaller rooms where experiments were carried out in which, on rainy days, the silence of the dark and gloomy interiors was interrupted by the sound of leaking rainwater being caught in buckets.

Lower circulated among the several surgeons assisting all of them with their research projects and there met Shumway, who turned out to be a kindred spirit.

Norman E. Shumway was born in Kalamazoo, Michigan in 1923 and raised in Jackson, Michigan. His career as an attorney was cut short after just one year of prelaw studies at the University of Michigan by army service in World War II. Recognizing that the infantry was not particularly attractive with a shooting war going on, he took the medical training opportunity presented by the Army with little vacillation. His premedical schooling was in Texas and his medical school training was at Vanderbilt University in Tennessee from which he graduated in 1949. He began his residency at the University of Minnesota graduate program in surgery.

However, after two years, Shumway was required to return to the service during the Korean conflict due to the schooling he had accepted from the government. After another couple of years, he was back at the University of Minnesota.

Norman Shumway
in 1958

Richard Lower
and friend

Edward Stinson
on left

Owen Wangensteen, M.D. was the then famous chief of surgery. Although Wangensteen was a general surgeon, Minnesota was the central hub for open-heart surgery with C. Walton Lilleihei, M.D. leading the clinical effort using cross-circulation and mechanical heart-lung support and F. John Lewis, M.D. leading the effort in the use of total-body hypothermia.

Wangensteen's surgical trainees formally matriculated in a doctoral program. Shumway's mentor was F. John Lewis, and therefore Shumway's doctoral research was on the effects of hypothermia on the heart. Specifically, Shumway studied the ventricular fibrillation threshold showing that as the temperature fell, less current was needed to cause the heart to fibrillate.

However, after five years of training, Shumway felt the urge to move on without taking the rotation through Dr. Wangensteen's service, which in practical effect meant not taking the traditional chief residency.

Eschewing the academic life temporarily, Shumway initially began a private clinical practice in partnership with an older surgeon in Santa Barbara, California in 1957. By all accounts, it was not a match made in heaven, and Shumway moved again to Northern California.

Shumway's academic choices were between the University of California and Stanford-Lane in San Francisco. But Shumway recognized that UCSF was not available to him when during his interview with the department chief, Dr. Leon Goldman, Dr. Goldman fell asleep. Shumway quietly left to try his luck with Stanford.

The prospects for a young cardiac surgeon breaking in at Stanford-Lane were only minimally brighter than at UCSF. Shumway was offered running the kidney dialysis machine and all the private practice he could hustle. In real terms, the latter meant taking calls for surgeons on vacation. There was little doubt that Dr. Frank Gerbode, Stanford's established heart surgeon, was not offering Shumway any openings at Stanford in heart surgery.

The opportunity for Shumway arose from an unlikely source - Dr. Ann Purdy. Purdy was one of Stanford's pediatric cardiologists and the wife of Dr. Emil Holman, the long-time chief of surgery at Stanford. Purdy had been disappointed in her professional relationships with Gerbode and Dr. Saul Robinson, another pediatric cardiologist, and moved her base of operations to the Children's Hospital in San Francisco. Roy Cohn, who had been working with Purdy on noncardiac congenital defects in children, suggested that he might be the appropriate surgeon to team with Shumway to perform heart surgery at Children's Hospital. To that end, Cohn provided funds to purchase the equipment necessary, got the referrals from Purdy, and prepared a team to perform the surgery.

When the program actually began, the line-up shifted when Cohn, perhaps busy with his clinical work, absented himself from the laboratory preparation stage. Shumway who, nominally, was to operate the heart-lung machine started running the operative team. Shumway teamed with Raymond Stofer, D.V.M. to work out the heart-lung machine and perfusion issues. Stofer, a master sergeant type in personality and appearance, was a veterinarian recruited by Stanford to oversee the operations of the surgical laboratory. Under his bluff exterior, Stofer was a master metal worker and in his private time a fine photographer. Although he had his own research projects, they were set aside when called upon to develop and operate the perfusion system. Under Shumway's direction, Stofer worked out an extraordinarily unadorned and spartan system with a minimum of gauges and monitors to watch, clean, or repair. The perfusion system was in marked contrast to the complex oxygenating system Gerbode's perfusionists and anesthesiologists had constructed and had become use to. This simplicity was to be a trademark of

Shumway's conceptual approach to surgical advances.

Lower was by then collaborating with Shumway, and when the time came for the first clinical cases, the group packed the equipment in a moving van and moved lock, stock, and barrel from the Stanford-Lane laboratories to the Children's Hospital operating room. Shumway's and Cohn's first case was an atrial septal defect in a young woman which was corrected under total-body hypothermia. After the surgery, the operating equipment was all packed up and moved back to Stanford-Lane. There were three more cases done at Children's Hospital before the school and Shumway moved to Palo Alto.

The key cardiac surgical question of the day was how to protect the heart during heart surgery. While some procedures could be carried out with the heart perfused and beating, greater accuracy in intraoperative diagnosis and repair could be gained with the heart "arrested" and the field relatively dry. Other procedures necessitated opening the aorta and thus the coronary arteries would not be perfused naturally. This was the most demanding situation. Two methods were then current: 1) use catheters and perfuse the coronary arteries and 2) use potassium arrest. Neither technique was particularly satisfactory. The first method cluttered the field with catheters and was fraught with mechanical perfusion problems. The second method gained no time for the surgeon and eventually was shown to be contraindicated.

Shumway and Lower tackled this problem in the laboratory, exploring an idea Shumway derived from his hypothermia experience. It was called "topical hypothermia." The experimental animal's body temperature was reduced using the perfusion equipment to about 32 degrees centigrade, while catheters were sutured around the edge of the opened pericardium which in turn had been sutured to the edges of the sternal wound to form a cradle. Ice cold saline then continuously flowed into the pericardial cradle, circulated around, and was then continuously sucked out. The technique limited further cooling only to the heart. The aorta was then cross-clamped so that no blood was flowing through the coronary arteries. After a period of time, the aorta was unclamped, blood flow restored, and the heart defibrillated with an electric shock. After a period of support the animal could maintain its circulation on its own and the heart-lung machine was discontinued.

Successful experiment after experiment were accomplished. The technique was published in "Selective Hypothermia of the Heart in Anoxic Cardiac Arrest," *Surgery, Gynecology, and Obstetrics* (1959; 109:750). All during the initial studies, Lower dutifully performed autopsies on all the hearts to obtain ventricular muscle tissues to study histologically. Lower routinely cut across the base of the atria to excise the heart.

As the cardiac arrest time got longer and longer, Lower and Shumway started discussing what they could do to pass the time of the cardiac arrest. All sorts of fantasies were indulged in while waiting. They considered bench heart surgery where the cooled heart was taken out and operated upon on a figurative back bench, replacing parts and suturing defects under ideal operating conditions.

To this end, Lower began experimenting with autotransplantation, wherein the heart was excised and sutured back in. Lower used the same technique in excising the heart for the operation as he had for excising the heart during the postmortem examinations. He cut through the base of the atria and then the pulmonary artery and aorta separately. The heart was excised and placed in an iced saline bath and then sutured in again. However, Lower had no successful autotransplant operation despite many attempts because of the fragile nature of the experimental animal's aorta. There was insufficient tissue to manipulate the heart autotransplant in the canine model.

Lower was then moved to attempt heart transplantation. He postulated that the hearts of both the donor and the recipient could be excised such that there would be surgically adequate margins to suture the heart back together with less technical wizardry demanded. That proved to be true. So it was that Shumway's hypothermia experiments led to Lower's thoughts about how to pass the time during the experiment to the first successful heart transplant operation in December 1959.

Allen, the department chairman, was concerned about the publicity and the fact that the animal's wound had become infected. However, Lower and Shumway wisely permitted the animal to survive the postoperative period and in seven days, the animal expired. The histological sections showed the classic pattern of cellular rejection with periarterial lymphocytic infiltration.

Lower, Stofer, and Shumway successfully carried out several more transplants during the spring and summer of 1960 with survival as long as three weeks. In October 1960, Lower presented his results at the Surgical Forum of the annual meeting of the American College of Surgeons: "Studies on Orthotopic Homotransplantation of the Canine Heart," *Surgical Forum* (1960; 11:18). There were very few listeners to Lower in the audience that day. Indeed, Watts Webb, M.D., the then leading researcher on heart transplants, gave a summary talk on transplant methods and simply said to the audience that he had heard that someone had presented a paper on a successful heart transplant at the meeting.

During the summer of 1960, Dong and Edward J. Hurley, M.D. both arrived at Stanford. Hurley was a Stanford medical alumnus and surgical resident who wanted cardiac surgery experience with Shumway. Shumway continued to build his practice as the cardiac surgeon at Stanford Palo Alto. Stofer was still moving the heart-lung equipment from the experimental laboratory to the clinical operating room, but the distance was considerably shorter than it was in San Francisco. In Palo Alto, the two operating rooms were at least on the same floors, albeit in different but connected buildings. Nonetheless, the fact that one heart-lung machine was sufficient to take care of both Shumway's clinical practice and the experimental laboratory indicates that Shumway still had a long way to go in the way of cardiac surgery referrals. Hurley and Dong were assigned to exploring heart autotransplantation to get an experimental model of the transplanted heart to examine how well it would function after allografting. Before Lower would move on to further his training, he was able to transplant a heart after seven hours of cold storage. Dong attempted to preserve hearts for longer than that period with a variety of perfusion techniques, but the conclusion remained the same: Shumway's cold storage technique could not be improved upon at the time.

For months Hurley suffered failure after failure with the canine autotransplant model. The failures for the most part were due to bleeding at the aortic suture lines. The entire laboratory was feeling the effects of the frustrating experience. Hurley longed for the luxury of having excess tissue margins with which to sew. Other animal models, sheep, swine, baboons, and calves were considered because their aortic tissues were thought to be of tougher material. It was finally decided to try the calf as a model. One consideration was that there was placental cross-circulation in some calf twins which might result in tolerance to the sibling's transplanted organ. The cross-circulated twin is called a freemartin.

However, the calf model presented problems never encountered with the canine model. One was obtaining blood for priming the heart-lung machine and for post-operative transfusions. The solution consisted of Hurley, Dong, Stofer, and laboratory technicians driving down to the nearest slaughter house which was in San Jose, California with bottles and large-bore plastic tubes in hand to get blood from freshly slaughtered animals on the mornings of the operations. The Stanford team put on rubber boots and aprons and stood next to a 2000 pound animal with its hind legs trussed up so that the animal towered above them. The external jugular vein would bulge visibly. An incision was made over the vein and the large-bore tubes were placed carefully and taped. One had to be careful else the tube would slip and the blood escape in a torrent.

Another was the fact that calves had to be kept upright because of the gas formation in their stomachs. Harnesses had to be developed to do that after the operation as a result of a couple of the animals dying from the "bloat."

Exploring tolerance with a freemartin transplant was quickly abandoned because the freemartin twin which would be the recipient was always the "runt" of the twins. It did not tolerate perfusion. Hurley turned to autotransplants in the calf. The aorta in the calf is definitely better tissue to reapproximate than the canine aorta. One day after several near misses, it looked like Hurley had a winner. Shumway stuck his head in the door and asked Hurley how it was going. Hurley had just taken off the aortic cross-clamp and expected the reperfusing heart to turn from blue to red. Nothing happened. A harried Hurley with Shumway looking over his shoulder found to his chagrin that the heart's pulmonary artery and aorta had been sewn to the distal aorta and pulmonary artery, respectively. This can occur easily in the calf because the vessel walls in contrast to both human and canine vessels are similar in thickness.

The calf studies ended when Hurley, after nursing one animal 48 hours postoperatively, went home to sleep and came back only to find the calf had strangled itself on its harness. Swallowing his surgical pride, Hurley asked Shumway to help on the next canine autotransplant which he did. And the animal was the first of several thereafter which Hurley operated on to survive indefinitely: "Isotopic Replacement of the Totally Excised Canine Heart," *Journal of Surgical Research* (1961; 2:90).

Hurley moved on in his training in 1962 and Dong was Shumway's cardiac resident and laboratory fellow. In the laboratory, Dong showed that the cardiovascular function shortly after autotransplantation and two years after autotransplantation were within normal limits. The denervation which is attendant to transplantation would pose no insurmountable barrier to heart allografting: "Performance of the Heart Two Years After Autotransplantation," *Surgery* (1964; 56:270).

In 1963, the musical chairs continued. Dong finished his year as cardiac surgery resident. Lower returned to Stanford and was stationed at the Palo Alto-Veterans Administration Hospital. While there were several lines of investigation in the laboratories, Lower and Dong were looking to extend the survival of allografted hearts. Specifically, they were looking for noninvasive parameters of cardiac rejection to test the hypothesis that specific treatment for rejection episodes only could reverse the episode and minimize the side effects of drug toxicity on the one hand and infection on the other.

Those parameters were found in the electrocardiogram, a decrease in the R-wave voltage. The rejection crises could be reversed with pulse treatment of antirejection drugs: "Suppression of Rejection Crises in the Clinical Homograft," *Annals Thoracic Surgery* (1965; 1:645).

Dong left Stanford in 1964 to enter the Air Force to fulfill his military obligations.

Lower presented the long-term results of cardiac homografts at the February 1965 Annual Meeting of the Society of University Surgeons. His longest survivor was still living at eight months after transplantation:

"Long term Survival of Cardiac Homografts," *Surgery* (1965; 58:110). The paper was given at the main sessions with an attendance which was significantly greater than the attendance in 1960.

Hurley moved on to the University of California Medical School at Davis, California. Lower went to the Medical College of Virginia. Dong returned to Stanford in 1966. Shumway prepared for the clinical applications of heart transplantation.

Epilogue

Shumway's first human transplant took place on January 6, 1968 at Stanford University Hospital. Edward B. Stinson, M.D. was then a member of the operating team and subsequently has taken a leading role in the continuation of the transplant program at Stanford. Philip Caves, Ch.B. and Margaret Billingham, M.D. introduced probably the most important single diagnostic tool for the monitoring of cardiac rejection, the endomyocardial biopsy. Bruce Reitz, M.D. performed the first successful heart-lung transplant while at Stanford. Philip Oyer, M.D., Ph.D. was the first to use a left ventricular assist device as a bridge to transplantation with a favorable outcome after transplantation.

As of May 9, 1991, 687 heart transplants have been performed on 615 patients at Stanford. The one-year and five-year survival rates on the last 418 patients are 81 percent and 61 percent, respectively. The longest surviving patient was transplanted January 3, 1970 and is doing well. According to the Heart Transplant Registry, the total number of heart transplant operations performed worldwide to date was 16,448. The total number of active heart transplant teams was 177.

CURRICULUM VITAE

Norman Edward Shumway

PERSONAL

Born:	February 9, 1923; Kalamazoo, Michigan

EDUCATION

1949	Vanderbilt University, M.D.
1956	University of Minnesota, Ph.D.

MILITARY SERVICE

1943-46	U.S. Army
1951-53	U.S. Airforce

BOARD CERTIFICATION

1957	American Board of Surgery
1958	American Board of Thoracic Surgery

POSITIONS

1954-56	Postdoctoral Research Fellow, National Heart Institute University of Minnesota
1957	Special Trainee, National Heart Institute, University of Minnesota
1959-62	Established Investigator, American Heart Association Stanford University
1958-59	Instructor in Surgery, Stanford University
1959-61	Assistant Professor of Surgery, Stanford University
1961-65	Associate Professor of Surgery, Stanford University
1964-74	Chief, Division of Cardiovascular Surgery, Stanford University
1965-	Professor of Cardiovascular Surgery
1974-	Chairman, Department of Cardiovascular Surgery, Stanford University
1976-	Frances and Charles D. Field Professor and Chairman, Department of Cardiovascular Surgery, Stanford University

PROFESSIONAL SOCIETIES

- American Surgical Association
- American Association for Thoracic Surgery
  - 1986-87 President
- Society of University Surgeons
- American College of Surgeons
- Society of Thoracic Surgeons
- Halsted Society
- Pacific Coast Surgical Association

San Francisco Surgical Society
American College of Cardiology
American College of Chest Physicians
Samson Thoracic Surgical Society
Society for Vascular Surgery
Santa Clara County Medical Society
Medical Society of the U.S. and Mexico Societe Internationale de Chirurgie
The Society of Thoracic and Cardiovascular Surgeons of Great Britain and Ireland
The Cardiac Society of Australia and New Zealand
Honorary Member, Canadian Cardiovascular Society
Alpha Omega Alpha
American Society of Transplant Surgeons
Western Association of Transplant Surgeons

AWARDS

1971	The Rene Leriche Prize, International Society of Surgery
1972	First recipient, Texas Heart Institute Medal
1975	Docteur honoris causa, Nancy University, Nancy, France
1976	Cameron Prize in Practical Therapeutics University of Edinburgh Faculty of Medicine, Scotland
1977	Honorary Degree of Doctor of Science, University of Chicago
1979	Honorary Degree of Doctor of Science, Pomona College Claremont, California
1979	Honorary Degree of Doctor of Science, Wittenberg University Springfield, Ohio
1980	Honorary Fellowship of Royal College of Surgeons of England
1981	Alumnus Honoris Causa Distinguished Achievement Award Baylor University College of Arts and Sciences
1982	International Recognition Award, Heart Research Foundation New York, N.Y.
1982	Gold Heart Award, American Heart Association, Dallas, Texas
1983	Dottore Honoris Causa, University of Torino, Turin, Italy
1983	Honorary Fellowship, The Royal College of Physicians and Surgeons of Glasgow
1983	Distinguished Alumnus Award, Vanderbilt University
1984	Sheen Award
1985	Benjamin J. Cory, M.D. Award, Santa Clara Valley Medical Center
1985	Outstanding Achievement Award, University of Minnesota

1986	Michael E. DeBakey Award, Michael E. DeBakey International Surgical Society, Melbourne, Australia
1986	Honorary Fellowship, Royal College of Surgeons of Edinburgh
1986	Rudolph Matas Award in Cardiovascular Surgery, Tulane University
1986	Ellen Browning Scripps Society Award, La Jolla, Callifornia
1986	The Trustees Medal for Distinguished Achievement Massachusetts General Hospital
1987	American Medical Association Scientific Achievement Award
1988	La Medaille Interanationale Lannelongue, Academie de Chirurgie Paris, France
1988	Albion Walter Hewlett Award, Stanford University School of Medicine
1988	Bayer Cardiovascular Research Mentor Award, New York, N.Y.
1989	Honorary Degree of Doctor of Science Mount Sinai School of Medicine
1990	Cedars-Sinai Medical Center Theodore E. Cummings Prize Los Angeles
1990	Albion O. Bernstein, M.D. Award Medical Society of the State of New York

PUBLICATIONS

Total: 478

CURRICULUM VITAE

Eugene Dong

PERSONAL

Born:	March 26, 1933
Citizenship:	United States
Office Address:	Department of Cardiovascular Sugery Stanford University Stanford, California 94305

MILITARY SERVICE

1964-66	Captain, MC, U.S.A.F., Chief, Research Services Division, Aerospace Medical Laboratory (Clinical), Wilford Hall USAF Hospital, Lackland AFB, Texas

EDUCATION

1949	Salinas Union High School
1949-50	Hartnell College, Salinas, California
1955	University of California Berkeley, Physiology, A.B. (with Highest Honors)
1959	University of California at San Francisco, M.D.
1981	Santa Clara University, Santa Clara, California, J.D.

POSITIONS

1959-60	Bellevue Hospital, First Medical Division Columbia University, New York
1960-64	Cardiac Surgery, Stanford Medical Center
1960-62	Post-doctoral Research Fellow, National Heart Institute Stanford Medical Center
1962-64	Post-doctoral Research Fellow, American Heart Association Stanford Medical Center
1966-67	Instructor in Surgery, Stanford University School of Medicine
1967-71	Assistant Professor of Surgery, Stanford University School of Medicine
1967-72	Established Investigator, American Heart Association Stanford Medical Center
1971-72	Associate Professor of Surgery, Stanford University School of Medicine
1972-	Associate Professor of Cardiovascular Surgery Stanford University School of Medicine
1975-76	Chief and Surgeon, Department of Cardiovascular Surgery Palo Alto Veterans Administration Hospital, Palo Alto, California
1975-76	Board of Medical Quality Assurance, Examiner

1977-	Consultant: commercial and scientific data processing
1978-	Vice President, A1 Ambulance Service, Inc., Salinas, CA
1981-	Consultant: medical malpractice litigation, scientific fraud, emergency vehicle services and antitrust evaluation of professional ethics codes
1981-	Member, State Bar of California admitted to practice: California State Courts Federal District Courts Northern District of California Eastern District of California

PROFESSIONAL SOCIETIES

Phi Beta Kappa

Society of the Sigma Xi, associate

Alpha Omega Alpha

American Association for the Advancement of Science,
Santa Clara County Medical Society

California Medical Association

American Society of Transplant Surgeons

American Society of Law and Medicine

PUBLICATIONS

Total: 1962-75: 105 articles (cardiac surgery, heart transplantation, artificial heart development, biomedical engineering and transplantation immunology)

Recent: Dong, E.: "The Legal Basis for Federal Prosecution of Science Misrepresentation as 'White Coat' Crime". In: Kilbourne, B.K. and Kilbourne, M.T., "the Dark Side of Science" 1983; San Francisco, American Association for the Advancement of Science, Pacific Division

Dong, E. and Andrepoulos, S.A., "Heartbeat", 1978. New York, Coward, McCann and Geoghegan, Inc. (A novel concerning the ethics of nuclear fuel powered artificial hearts)

Dong, E. "The Federal False Claims Act and Scientific Fraud" Northern California Medicine, (In Press)

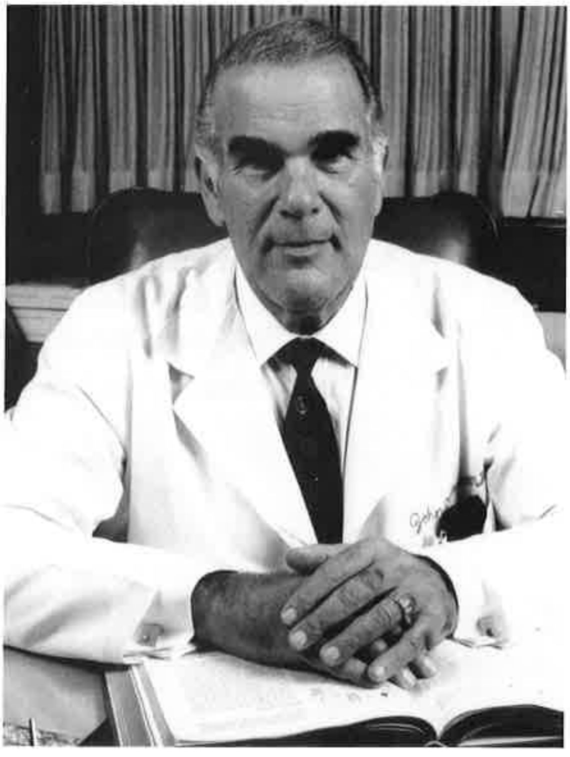
A TRANSPLANT ODYSSEY

John S. Najarian

Address: University of Minnesota Hospital
516 Delaware Street S.E.
Box 195 UHMC
Minneapolis, Minnesota 55455

John S. Najarian

1967



1991

A TRANSPLANT ODYSSEY

John S. Najarian

"Tell me, muse, of the man of many resources who wandered
far and wide...and learned the thoughts of many men,
and on the sea he suffered in his heart many woes."
--Homer, *The Odyssey* (Book I, Line 1)

When I was originally asked by Paul Terasaki to write a personal recollection of my experiences in transplantation, I must admit that I was quite reluctant. It would be hard to put together the precise times and the specific details. I wanted to be as accurate as possible, but an involvement in transplantation dating back 35 years leaves some dark crevices in one's mind that make total recall difficult. However, those of us who know Paul Terasaki know how persistent he is; even though I continued to object to writing such a personal recollection, his insistence and our longtime friendship persuaded me to at least make an attempt. I decided to entitle this article "A Transplant Odyssey," since I look on my 35 years as a saga of, first, curiosity, then preparation, followed by research and clinical progress. I will first overview the beginnings of my interest in transplantation in the context of my academic career and then focus on specific areas of accomplishment. In the course of my journey in this Homeric field, I have traveled many fascinating byways.

My Interest in Transplantation

Following medical school at the University of California at San Francisco, I spent one year as a surgical intern before entering the United States Air Force in 1953. I was the Division Surgeon for the 34th Air Division based at Kirtland Air Force Base in Albuquerque, New Mexico. During that time, I had the opportunity to participate as a volunteer part-time surgeon at the Lovelace Clinic in Albuquerque between my administrative and medical duties with the Air Force. It was this experience that reinforced my resolve to become an academic surgeon. At that point, I felt there were two main horizons in academic surgery: cardiac surgery and transplant surgery. It was apparent, with the advent of the pump oxygenator, that open heart surgery would soon become a reality - with only technical details to be developed in the future, such as better pump oxygenators and better mechanical valves. On the other hand, tissue transplantation in the early 1950s was really not yet even on the clinical horizon. Thus, I chose transplantation because it presented the greater research challenge. It soon became apparent that a solid background in immunology would be necessary to develop a foundation for a career in this exciting new field of reconstructive and restorative surgery.

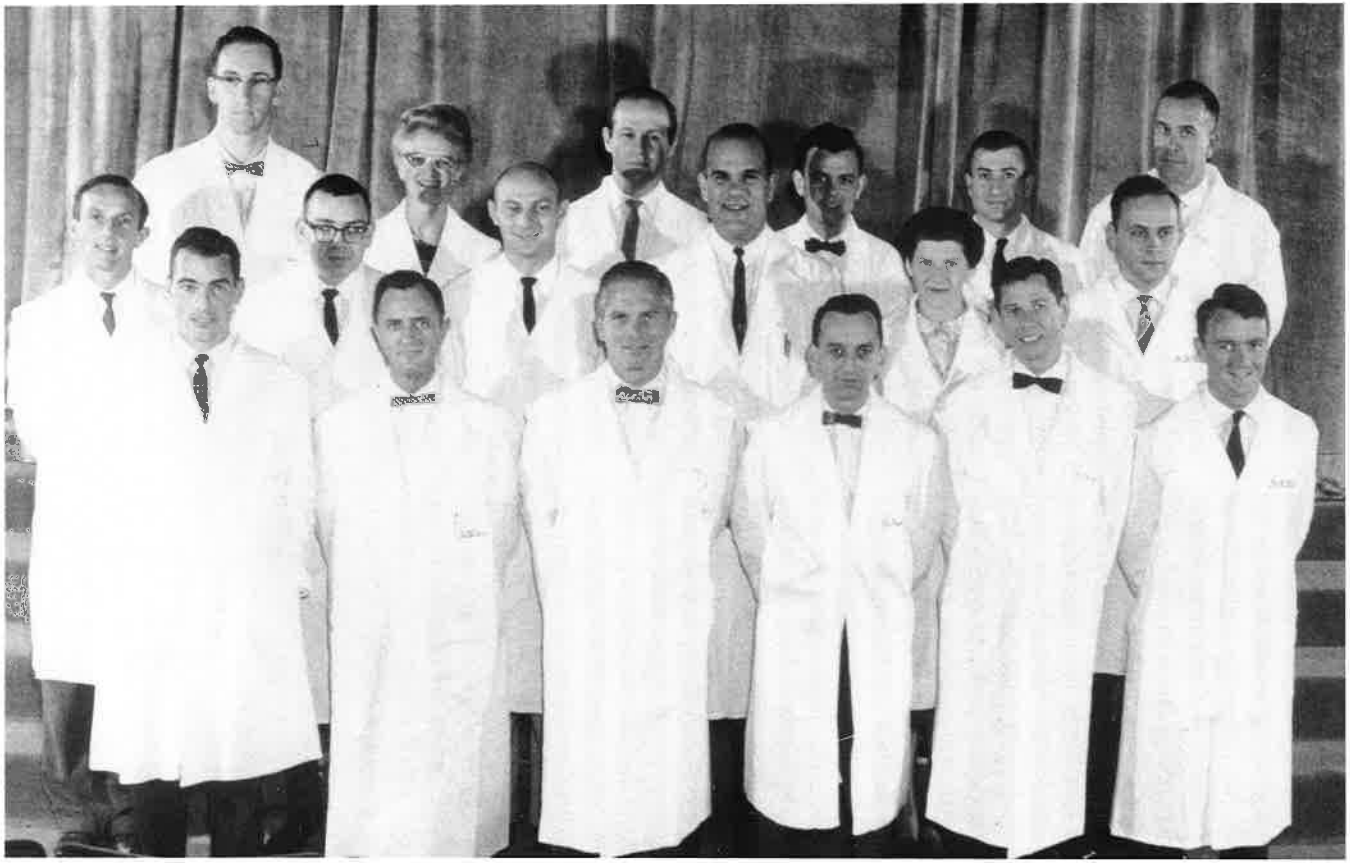
I initially contacted Sir Peter Medawar in 1959, in London, and although I could be accepted for a position in his laboratory, I would need to wait one year after my chief residency. Looking for an immediate opportunity to study immunology, I was fortunate enough to be offered a position with Frank Dixon in immunopathology at the University of Pittsburgh. My immediate mentor, Joseph Feldman, and I worked together on the problems associated with cellular immunity. The early 1960s dogma was that transplantation rejection was strictly an event of cellular immunity and that humoral immunity had very little effect, except in hyperacute and acute rejection in a presensitized individual or in heterotransplantation. I felt I needed to know more about cellular immunity, and the best model to study it was the tuberculin reaction. One of my greatest thrills was publishing my first paper in the *Journal of Experimental Medicine*, on passive transfer of tuberculin sensitivity by tritiated thymidine-labeled lymphoid cells (1). Eventually I had a second article in the *Journal of Experimental Medicine* in which Joseph Feldman and I looked at passive transfer of transplantation immunity - not only with tritiated lymphoid cells but with lymphoid cells in millipore chambers (2). From this work, we concluded that some information was being passed from sensitized cells to naive cells through the millipore chambers, instructing these cells in the tuberculin reaction. We hypothesized that a similar mechanism functions in the transplantation reaction.

While this study was going on, I also participated in research with Frank Dixon. We looked at the immunologic tolerance to maternal tissues produced by alterations in placental permeability. In October 1961, we presented that work at the Surgical Forum of the American College of Surgeons (3). This was a very meaningful meeting for me. Until then, most of my papers had been presented at the federation meetings of the American Association of Immunologists or the Society for Experimental Pathology. But this was the first time I had a chance to interact with other surgeons who were also interested in transplantation immunology. I clearly remember my meeting with Sir Roy Calne, who was presenting a paper on work he had done at the Peter Bent Brigham and Women's Hospital on azathioprine's effect on extending kidney allograft survival in dogs. It was evident that this extremely exciting finding might eventually be applied to humans, although most classical immunologists I knew at that time felt it was too soon to use this agent in human organ allotransplantation.

Fortunately, however, the surgeons were cavalier enough to go ahead and show that azathioprine - and subsequently, prednisone as well, following the work of Willard Goodwin and others - would be very acceptable immunosuppressive agents. Moderately good results were achieved. For the first time, kidney allotransplantation was accomplished without the use of potentially lethal techniques such as total body irradiation.

Meanwhile, I continued my immunopathology work with Joseph Feldman and Frank Dixon at the Scripps Clinic and Research Foundation in La Jolla, California. I studied graft-versus-host disease in adult mice (4) and did further work on passive transfer of transplantation immunity in inbred guinea pigs (5). In addition, we extended our passive transfer studies to encompass passive transfer of contact sensitivity by tritiated thymidine-labeled lymphoid cells (6). Two papers were published in the *Journal of Experimantal Medicine*. Later, I published a paper on the dynamics and quantitative analysis of passively transferred tuberculin hypersensitivity in the *Journal of Immunology* with Joseph Feldman (7).

More and more it appeared as though I would stay at the Scripps Clinic and Research Foundation. However, I was anxious to return to surgery. Back at the University of California at San Francisco, I was offered a position as Assistant Professor and Director of Surgical Research Laboratories and an opportunity to establish a transplant program. So I left La Jolla in 1963. At that time, the only program on the west coast that had done kidney transplants was at UCLA under Willard Goodwin. I started the second west coast program in 1963 at UCSF. I also continued my laboratory work in immunology. As the kidney transplant program progressed well, I began to direct my research focus at the challenge of heterotransplantation. Two PhD candidates worked in my laboratory, Robert Perper and Kent Cochrum, and together we wrote several papers on heterotransplantation. Perper wrote his PhD thesis on heterotransplantation.



John S. Najarian, M.D., as a senior fellow and associate in tissue transplantation immunology at the Scripps Clinic and Research Foundation/NIH in 1962

In 1966, I was promoted from Assistant Professor to full Professor and Vice Chairman of the Department of Surgery. I was given this promotion primarily to counteract my active recruitment by 10 institutions to become Chair of their surgery departments. This very nice promotion made it easier for me to stay in San Francisco and continue my clinical kidney transplant work and transplant immunology research.

I must give some of the credit for initiating our kidney transplant program in San Francisco to Tom Starzl. After I returned to San Francisco in 1963, having been away from clinical surgery for three years, I paid a visit to Tom in Denver and observed a kidney transplant at his institution. I then felt much more comfortable performing our own first kidney transplant in San Francisco. Tom and I have enjoyed a professional as well as social comradeship ever since. We have had many opportunities for active public and private debate on a variety of transplant issues. Although very spirited many times, we have always ended on a note of friendship, which I have appreciated and valued over the past 30 years.

In 1964, when Bert Dunphy became Chairman of the Department of Surgery at UCSF, he brought with him a young assistant professor who had trained with him in Oregon. He wanted to find a place for him on the staff. His name was Folkert (Fred) Belzer, and he was interested in transplantation. Since Fred had no immunological training, I felt he should work in an area suited to his background in preservation. Fred worked long and hard, investigating various preservation studies. The discovery of the final preservation solution that would allow for perfusion of stored organs was a classic case of serendipity. Fred had obtained dog blood to prepare a plasma solution for preservation, but because of a commitment that evening, did not have time to use the plasma for organ perfusion. So, he simply stored the plasma overnight in the refrigerator. The next morning, he was disappointed to find a "cloudy" plasma. He centrifuged it to remove this material - which proved to be cryoprecipitated lipids - and used the clear plasma for perfusion. For the first time, perfusion was successful without damage to the kidney! Because a prepared mind took advantage of what appeared to be a mishap, cryoprecipitated plasma became the key to perfusion preservation.

Now, with a successful preservation technique, sufficient time was available for cold ischemia of the harvested donor organ. With more time permitted by preservation, donors and recipients could be better matched. Rose Payne of Stanford, who was also working with us at UCSF, was active in describing leukocyte antigens, leading the way toward tissue typing. Thus, tissue typing–a field then coming into its own–could be properly applied to match cadaver donor organs with appropriate recipients.

With Rose Payne and Herb Perkins of the Irwin Memorial Blood Bank of San Francisco, I co-authored an article on the compatibility of seven leukocyte antigens in renal homografts (8). What a wonderful opportunity to work with someone like Rose Payne, one of the pioneer investigators to define leukocyte antigens, along with Jon Van Rood, and eventually Paul Terasaki, whose work on graft-versus-host disease was the only way I'd known him before. Tissue typing had really come full circle and had become a very important part of organ transplantation.

In 1967, I accepted the position of Chairman of the Department of Surgery at the University of Minnesota. Looking back at the last 24 years here, I have had the privilege to contribute, both experimentally and clinically, to these areas: xenotransplantation; the development of Minnesota antilymphoblast globulin; kidney, pancreas, and islet cell transplantation in diabetic patients; kidney transplantation in infants and children; techniques for diagnosis and treatment of opportunistic infectious disease; early attempts at enzymatic transplantation through kidney transplantation in patients with Fabry's disease and Gaucher's disease; the validation of cyclosporine through a prospective randomized clinical trial; and the training of transplant surgeons. Next, I will briefly examine some of these areas, particularly the path that I was able to follow, in some degree of chronological order.

Xenotransplantation

As mentioned before, my interest in xenotransplantation began in 1964 when working with two PhD candidates in my laboratory, Robert Perper and Kent Cochrum. My first publication on this subject appeared in *Transplantation* in 1966 (9), co-authored by Perper. We looked at widely divergent (discordant) species and found a very rapid rejection process, which occurred within a matter of minutes and was primarily mediated by humoral mechanisms. We then turned our attention to closely related (concordant) species, primarily the goat and sheep. In that species combination, we observed kidney transplant rejection that very much simulated allograft rejection, but was slightly more rapid and primarily involved cellular immunity (10). Eventually, we were able to passively transfer heterotransplantation immunity with serum alone (11) and could actually localize and quantitate the transplantation antibodies at the site of rejection (12). Finally, still in San Francisco, we were able to find host fixation and kinetics of anti-tissue antibodies, as published in *Transplantation* in 1968 (13).

Some of my early PhD candidates at the University of Minnesota, such as Alan Shons, became involved with the heterotransplantation story. In 1970, we showed we could prolong heterograft survival by electrophoretic extraction of preformed antibodies (14). In addition, we eventually inhibited complement, coagulation, and antibody synthesis and showed that these manipulations could prolong heterograft rejection (15). We even extended our studies to determine if a similar effect of preformed antibodies was present in humans. We perfused human blood and plasma through dog kidneys and determined that similar preformed antibodies were present in human-against-dog as well as dog-against-human tissues.

Saint Mary's Hospital in San Francisco, May 20, 1965

We recently began a more sophisticated re-examination of xenotransplantation. We are looking at the endothelial response and the activation of the coagulation and complement cascades. These studies are being done in our surgery laboratories, as well as in collaboration with Fritz Bach in the immunobiology laboratories. We currently have a program project grant pending in xenotransplantation. Our hope is that xenotransplantation will help solve the organ shortage, which continues to be most pressing and limits progress, especially now that transplantation has become so successful.

Minnesota Antilymphoblast Globulin (MALG)

While still at UCSF in 1966, I began working with antilymphocyte globulin as an immunosuppressive agent. We injected horses housed in barns at Golden Gate Park and first reported our technique for purifying large quantities of antilymphocyte serum in the *Proceedings of the Society for Experimental Medicine* in 1967 (16). That same year, shortly after arriving in Minnesota, I began making antilymphocyte globulin here. It became Minnesota antilymphoblast globulin (MALG), since we were using cultured lymphoblasts to stimulate our horses to produce polyclonal antilymphoblast globulin. We soon began using antilymphoblast globulin clinically and published our first paper on its clinical use in *Transplantation Proceedings* in 1969 (17).

Eventually, we improved our purification techniques and have since used MALG for induction therapy in most of our patients (we also use it to combat rejection episodes). In the early 1970s, our induction therapy, featuring MALG along with azathioprine and prednisone, resulted in kidney graft and patient survival rates at least 10 percent to 15 percent better than at institutions not using MALG. Subsequently, MALG has become quite popular; it is currently used by well over 100 different transplant institutions.

Transplantation in Diabetic Patients

When I came to the University of Minnesota, I was fortunate enough to find a very active new program in pancreas transplantation headed by William Kelley and Richard Lillehei. They had performed their first combined kidney and pancreas transplant in December 1966. After I arrived in July 1967, I joined the group and we performed nine additional kidney and pancreas transplants. We published a summary of this work in *Annals of Surgery*, and Richard Lillehei (18) presented it at the American Surgical Association that same year (1970). Although for a short time the kidney, the pancreas, or both functioned, rejection of one or both occurred sometime within the first few months. In only one of our patients did both organs function for more than a year; unfortunately, this patient committed suicide. This experience, however, showed us that both the kidney and the pancreas would function in Type 1 diabetic patients and that the pancreas functioned well, both as an endocrine and an exocrine organ.

We then declared a moratorium on pancreas transplants in diabetic patients, since we felt this was too much surgery for them. So in 1968, we began doing kidney transplants alone in diabetic patients. Since then, we have achieved kidney transplant results in diabetic patients that equal those of nondiabetic patients up to the first four or five years posttransplant; after that, given the effect of their continuing diabetes and its progressive triopathy, survival rates of diabetic and nondiabetic patients diverge. Perhaps most important, we convinced other transplant surgeons to do kidney transplants in Type 1 diabetic patients, who until then were undergoing neither transplantation nor dialysis. At the University of Minnesota, we have now done over 1,200 kidney transplants in Type 1 diabetic patients; in fact, diabetes mellitus is the single most common disease for which kidney transplants are done, both here and throughout the world.

We have learned, from our growing kidney transplant experience in diabetic patients, that eliminating their uremic retinopathy and neuropathy stabilizes the eyesight of two-thirds of the patients, as well as their neuropathy.

We began working on islet transplantation in the laboratory in 1969. Finally, we were able to show that it effectively treats diabetes in mice made diabetic with a streptozotocin administration. So, we returned to the clinical arena and started a series of islet cell transplants in diabetic patients. We presented these findings on some 24 diabetic patients to the Transplantation Society in 1974 (19). As a result of this first clinical islet cell allotransplantation experience, we could reduce a patient's insulin requirements but were never able to make a single patient insulin-independent. Therefore, we called a moratorium on this clinical series and went back to the laboratory once again. We started a new series of pancreas transplants in 1978, initially doing partial pancreas transplants, occluding the pancreatic duct with different polymers. Eventually, in some, we drained the pancreatic duct into the intestine or into the bladder - techniques still used to this day. We have now done over 400 pancreas transplants and are currently doing about 60 to 65 each year. The Director of our Pancreas Transplant Program, David Sutherland, founded the International Pancreas Transplant Registry in 1978, which currently totals 3,086 such operations (as of December 31, 1990).

From our pancreas transplant experience, we have found it is possible not only to stabilize the eyesight of diabetic patients but also to reverse some of the retinopathy after three years posttransplant. In addition, we have seen improvement in both their neuropathy and nephropathy. Thus, the triopathy of complications associated with diabetes can not only be stopped but in many instances, reversed - if caught early enough with a successful pancreas transplant.

Kidney Transplantation in Infants and Children

Working with pediatric nephrologists Donald Potter and Malcolm Holiday at UCSF, I became interested in transplantation in children. We reported our results in *Pediatrics* in 1970 (20). When I moved to Minnesota, I was fortunate to find a very strong Division of Pediatric Nephrology, headed by Alfred Michael and Robert Vernier. In addition, Michael Mauer and eventually Thomas Nevins and Blanche Chavers were involved in our pediatric kidney transplant experience. One of the first articles we wrote was on the recurrence of idiopathic nephrotic syndrome after kidney transplantation in *Lancet* (21). In 1974 (22), we reported on our first 100 children who received kidney transplants. Since then, I have had the opportunity to transplant over 500 children under the age of 16, 100 under the age of two, and 30 under the age of one. Eventually, we were able to show that children under the age of one were immunologically very reactive; our early disappointing experience with cadaver kidney transplants in these infants resulted in failure in three cases.

We subsequently began using living-related donors, including mothers, fathers, and older brothers and sisters. These living-related donor kidney transplants were successful. Our results with infants under the age of one now parallel our very best older subgroups: graft survival is over 90 percent at one year and over 85 percent at two years. Our most recent experience in infants was published in *Annals of Surgery* in 1990 (23). Hopefully, these favorable results in infants will persuade our colleagues to consider transplanting infants under the age of one, rather than having them wait on dialysis with the possibility of serious central nervous system consequences in some cases.

Opportunistic Infectious Disease

Within a year after arriving in Minnesota, I was fortunate enough to recruit Richard Simmons to join me in our transplant program. The establishment and success of many of our programs in transplantation could not have occurred without his help. It was with his interest in infectious diseases that we began to study the many fascinating opportunistic infections suffered by transplant patients. He was instrumental in much of the early work on the importance of Epstein-Barr virus (EBV) in the pathogenesis of lymphoproliferative disorders and malignant lymphomas in transplant patients. We were also indebted to the very diligent experimental and clinical studies by one of our residents, Douglas Hanto. From that point on, we have had a continuing interest in various opportunistic infections. Currently, we are working to improve techniques to diagnose and treat cytomegalovirus, EBV, and other viral and fungal infections. These studies are being done under the direction of David Dunn in our Department of Surgery and Henry Balfour, a virologist in the Department of Laboratory Medicine.

Enzymatic Transplantation

Quite fortunately, at the University of Minnesota, in collaboration with Robert Desnick and William Krivit, we were able to do some kidney transplants in patients with enzymatic deficiency diseases; namely, Fabry's disease and Gaucher's disease. Our first publication of this work, entitled "Correction of Enzymatic Deficiencies in Renal Transplantation: Fabry's Disease," was in *Surgery* in 1972 (24). In addition, we were able to see improvement in a patient with infantile Gaucher's disease simply through a kidney transplant. More recently, it has become evident that correcting these enzymatic deficiency diseases will probably require either a larger organ (such as a liver) transplant or possibly a bone marrow transplant. However, this early experience with treatment of enzymatic deficiency diseases was an interesting beginning to this important field. A summary of our results was reported in 1973 (25,26).

Validation of Cyclosporine

We were very fortunate at the University of Minnesota to obtain cyclosporine from Sandoz for a preliminary trial in 1979. At that time, we felt that a randomized prospective clinical trail was indicated to prove the efficacy of this immunosuppressive agent. This trial (27) demonstrated that cyclosporine remarkably reduced the number of rejection episodes and, thus, decreased the amount of prednisone required. As a result, the group receiving cyclosporine also experienced fewer infections. Our immunosuppressive approach evolved into the triple postinduction or maintenance therapy of cyclosporine, azathioprine, and prednisone, which is now used by almost all transplant institutions.

Training

The most important of our contributions in transplantation has been the opportunity to train many young transplant surgeons, who now fill posts in this country and abroad. We started a formal training program featuring a one-year, largely clinical experience: four months as a donor fellow, doing the shunt operations; then four months as a recipient fellow; and finally four months of research. Since then, our training program has evolved to two years: four months as a donor fellow, doing the shunt operations; four months as a kidney recipient fellow; four months as a liver recipient fellow; and four months as a pancreas recipient fellow. After these 16 clinical months, the last eight months are spent doing either laboratory or clinical research.

Richard L. Simmons, M.D., F.A.C.S.

Dr. John Najarian and Dr. David Hume on May 19, 1973, the tragic morning that David Hume died in an airplane crash.

In addition, from June 1980 through June 1988, I had the privilege of being the Chairman of the Education Committee for the American Society of Transplant Surgeons. We structured a training program in transplantation for all surgeons in this important field, so that they could eventually manage high-quality transplant programs.

The following is a list of all the transplant surgeons who have trained at the University of Minnesota:

	NAME	TRAINING DATE	CURRENT APPOINTMENT
1.	Richard Weil III, M.D.	Jan. - June 70	New York University
2.	David W. Kinne, M.D.	Jan. - June 71	Memorial Hospital, New York City
3.	Schrae LaPlante, M.D.	July - Dec. 71	West Virginia University
4.	Goren Lundgren, M.D.	Apr. - Dec. 70	Serafimer Hospital, Stockholm, Sweden
5.	Eduardo-Delphin Santiago, M.D.	1971-72	University of Puerto Rico
6.	Clive Callender, M.D.	1971-72	Howard University
7.	Claude DeShazo, M.D.	1972-73	University of Washington
8.	Luca Rattazzi, M.D.	1973-74	University of Washington
9.	Peter Spanos, M.D.	1973-74	Thessalonica, Greece
10.	Robert Casali, M.D.	1973-74	University of Arkansas
11.	Martin Mozes, M.D.	1974-75	Henry Ford Hospital, University of Illinois
12.	David E.R. Sutherland, M.D., Ph.D.	1974-75	University of Minnesota
13.	Richard J. Howard, M.D.	1975-76	University of Florida
14.	John G. Buls, M.D.	Jan. - Dec. 76	University of Minnesota
15.	George E. Merino, M.D.	1976-77	Private Practice, Las Vegas, Nevada
16.	George Kyriakides, M.D.	1976-77	Greece/Cypress
17.	Ramiro Garcia-Reyes, M.D.	1977-78	University Hospitals of San Diego, California
18.	Toni Hau, M.D.	1977-78	Germany
19.	Steven Jensik, M.D.	1978-79	Rush Presbyterian Hospital, Chicago
20.	Ronald Ferguson, M.D.	1978-79	Ohio State University
21.	Arthur J. Matas, M.D.	1979-80	University of Minnesota
22.	William D. Payne, M.D.	1979-80	University of Minnesota
23.	Caliann T. Lum, M.D., Ph.D.	1980-81	University of Texas, San Antonio
24.	Chuck Peters, M.D. (MGH)	1981-82	University of Texas, Houston
25.	Nancy Ascher, M.D.	1981-82	UCSF
26.	Bruce G. Sommer, M.D.	1981-82	SUNY Downstate
27.	Robert Gifford, M.D.	1982-83	Pennsylvania State University, Hershey
28.	Jock Simon, M.D.	1983-84	Howard University
29.	Frederick Bentley, M.D.	1983-84	University of Louisville
30.	William Nylander, M.D.	1983-84	Vanderbilt University
31.	William I. Lewis, M.D.	1984-85	Southern Illinois University
32.	Douglas Hanto, M.D.	1984-85	University of Cincinnati
33.	Philip Boudreaux, M.D.	1985-86	Oschner Clinic, New Orleans, Louisiana
34.	David Dunn, M.D., Ph.D.	1985-86	University of Minnesota
35.	Chris Johnson, M.D.	1985-86	University of Wisconsin, Milwaukee
36.	Timothy Pruett, M.D.	1986-87	University of Virginia, Charlottesville
37.	George Burke, M.D.	1986-87	University of Miami
38.	Carl Nohr, M.D.	1986-87	Royal Victoria Hospital, Montreal, Canada
39.	John Roberts, M.D.	1987-88	UCSF
40.	Mark Pescovitz, M.D.	1987-88	Indiana University
41.	Rainer Gruessner, M.D.	1988-89	Germany
42.	Samuel K.S. So, M.D.	1988-89	Washington University
43.	Paul Gores, M.D.	1988-89	University of Minnesota
44.	Kristine Koontz, M.D.	July - Nov. 89	Tulane University
45.	Alfredo Fabrega, M.D.	1988-90	University of Illinois, Chicago
46.	Daniel Frey, M.D.	1989-90	Louisiana State University
47.	Kenneth Brayman, M.D., Ph.D.	1989-91	University of Minnesota
48.	Francisco Escobar, M.D.	1989-91	Pennsylvania State University, Hershey
49.	Eugene Schweitzer, M.D.	1990-91	University of Baltimore
50.	Richard Perez, M.D.	1990-91	University of Minnesota (In training)
51.	Alan H.S. Cheung, M.D.	1990-91	University of Minnesota (In training)
52.	Giacommo Basadonna, M.D.	1991-92	University of Minnesota (In training)

Left to right: Dr. John Najarian, Lady Medawar, Dr. Fritz Bach; foreground: Sir Peter Medawar in 1982

Dr. Najarian – honorary fellowship at the Royal College of Surgeons, England, November 12, 1987

In closing, my transplant odyssey has been filled with highs and lows. In the research laboratory, there have been many accomplishments and many disappointments. But the sum total has always been on the positive side, as it has been clinically. We have been very pleased that, with our current immunosuppression and sophisticated tissue typing techniques, all solid organ transplantation now enjoys very high success rates. In addition, the establishment of a United States organization, the United Network for Organ Sharing (UNOS), enables organs to be harvested and shipped to the recipient who best matches the donor. In all, we have now transplanted over 3,500 kidneys, over 400 pancreases, over 300 livers, over 300 hearts, over 50 heart/lungs, and over 20 lungs at the University of Minnesota.

As I look to the future, I feel that the results will continue to get better, thanks to the newer immunosuppressive agents now being examined. Xenotransplantation, which looked like only a dream two decades ago, may be coming closer to reality as more researchers and clinicians become involved. Only through xenotransplantation, or through prevention or correction of the diseases that cause end-stage organ failure in the first place, can we solve the growing donor shortage.

(Left to right) Drs. Folkert Belzer, Oscar Salvatierra, and John Najarian, at the 27th Anniversary Celebration of the Transplant Program at the University of California at San Francisco in 1990.

REFERENCES

1. Najarian JS, Feldman JD. Passive transfer of tuberculin sensitivity by tritiated thymidine-labeled lymphoid cells. J Exp Med 1961; 114: 5:779.

2. Najarian JS, Feldman JD. Passive transfer of transplantation immunity. I. Tritiated lymphoid cells. II. Lymphoid cells in millipore chambers. J Exp Med 1962; 115:1083.

3. Najarian JS, Dixon FJ. Immunologic tolerance to maternal tissues produced by alterations in placental permeability. Surg Forum 1961; 12:101.

4. Najarian JS, Feldman JD. Induction of runt disease in adult mice by presensitized homologous lymphoid cells. Proc Soc Exp Biol Med 1962; 1001:1621.

5. Najarian JS, Feldman JD. Passive transfer of transplantation immunity. III. Inbred guinea pigs. J Exp Med 1963; 17: 3:449.

6. Najarian JS, Feldman JD. Passive transfer of contact sensitivity by tritiated thymidine-labelled lymphoid cells. J Exp Med 1963; 117: 5:775.

7. Feldman JD, Najarian JS. Dynamics and quantitative analysis of passively transferred tuberculin hypersensitivity. J Immunol 1963; 91: 3:306.

8. Payne R, Perkins HA, Najarian JS. Compatibility for seven leukocyte antigens in renal homografts: Utilization of microagglutination test with few sera. In: Curtoni ES, Mattuiz PL, Tose RM, Eds: Histocompatibility Testing, Denmark, RJ Schmidt, Vogens, 1967, 237.

9. Perper RJ, Najarian JS. Experimental renal heterotransplantation. I. In widely divergent species. Transplantation 1966; 4:377.

10. Perper RJ, Najarian JS. Experimental renal heterotransplantation. II. In closely related species. Transplantation 1966; 4: 6:700.

11. Perper RJ, Najarian JS. Experimental renal heterotransplantation. III. Passive transfer of transplantation immunity. Transplantation 1967; 5: 3:514.

12. Perper RJ, Najarian JS. Localization and quantitation of transplantation antibodies. J Immunol 1967; 99: 3:916.

13. Perper RJ, Najarian JS. Host fixation and kinetics of antitissue antibodies. Transplantation 1968; 6: 7:833.

14. Shons AR, Jetzer T, Mobert AW, Najarian JS. Prolongation of heterograft survival by electrophoretic extraction of preformed antibody. Surg Forum 1970; 21:263.

15. Moberg AW, Shons AR, Gewurz H, et al. Prolongation of renal xenografts by the simultaneous sequestration of preformed antibody, inhibition of complement, coagulation and antibody synthesis. Transplant Proc 1971; 3: 1:538.

16. Perper RJ, Okimoto JT, Cochrum KC, et al. A rapid method for purification of large quantities of antilymphocytic serum. Proc Soc Exp Biol Med 1967; 125: 2:575.

17. Najarian JS, Merkel FK, Moore GE, et al. Clinical use of antilymphoblast serum. Transplant Proc 1969; 1:460.

18. Lillehei RC, Simmons RL, Najarian JS, et al. Pancratico-duodenal allotransplantation: Experimental and clinical experience. Ann Surg 1970; 172: 3:405.

19. Najarian JS, Sutherland DER, Steffes MW. Isolation of human islets of Langerhans for transplantation. Transplant Proc VII: 1975; 1 (Suppl 1): 611

20. Potter D, Belzer FO, Rames L, et al. The treatment of chronic uremia in childhood. I. Transplantation. Pediatrics 1970; 45:432.

21. Hoyer JR, Raij L, Vernier RL, et al. Recurrence of idiopathic nephrotic syndrome after renal transplantation. Lancet 1972; 2:343.

22. DeShazo CV, Simmons RL, Bernstein DM, et al. Results of renal transplantation in 100 children. Surgery 1974; 75: 3:461.

23. Najarian JS, Frey DJ, Matas AJ, et al. Renal transplantation in infants. Ann Surg 1990; 212: 3:353.

24. Desnick RJ, Simmons RL, Allen KY, et al. Correction of enzymatic deficiencies by renal transplantation: Fabry's disease. Surgery 1972; 72: 2:203.

25. Desnick RJ, Allen KY, Simmons RL, et al. Fabry's disease: Correction of the enzymatic deficiency by renal transplantation. In: Bergsma D, Desnick RJ, Bernlohr R, Krivit W, Eds. Enzyme Therapy in Genetic Disease, Birth Defects: Original Article Series, Vol IX, New York, National Foundation 1973, 88.

26. Desnick SJ, Desnick RJ, Brady RO, et al. Renal Transplantation in Type II Gaucher disease. In: Bergsma D, Desnick RJ, Bernlohr R, Krivit W, Eds. Enzyme Therapy in Genetic Diseases, Birth Defects: Original Article Series, Vol IX, New York: National Foundation, 1973, 109.

27. Najarian JS, Ferguson RM, Sutherland DER, et al. A prospective trial of the efficacy of cyclosporine in renal transplantation at the University of Minnesota. Transplant Proc 1983; 15:1:438.

CURRICULUM VITAE

John S. Najarian

PERSONAL

Born: December 22, 1927; Oakland, California

Marital Status: Married; 4 sons

Office Address: University of Minnesota Hospital
516 Delaware Street S.E.
Box 195 UMHC
Minneapolis, MN 55455

EDUCATION

1948	University of California, Berkeley, A.B. with Honors
1952	University of California, San Francisco, School of Medicine, M.D.

MILITARY SERVICE

1953-55	Division Surgeon, 34th Air Division, United States Air Force Albuquerque, New Mexico

POSITIONS

1952-53	Internship, straight surgical, University of California, San Francisco, School of Medicine
1955-60	Residency, surgical, University of California, San Francisco, School of Medicine
1960-61	Special Research Fellow, Immunopathology University of Pittsburgh Medical School, National Institutes of Health
1961-63	Senior Fellow and Associate, Tissue Transplantation Immunology, Scripps Clinic and Research Foundation, National Institutes of Health
1963-66	Assistant Professor of Surgery, Director of Surgical Research Laboratories, Chief of Transplantation Service, Department of Surgery, University of California, San Francisco, School of Medicine
1966-67	Professor and Vice Chairman, Department of Surgery University of California, San Francisco, School of Medicine
1967-	Professor and Chairman, Department of Surgery University of Minnesota Medical School, Minneapolis
1970-71	Chief of Staff, University of Minnesota Hospital
1972	Board of Directors, Variety Club Heart Hospital
1986-	Regents' Professor, Jay Phillips Distinguished Chair in Surgery, Department of Surgery, University of Minnesota Medical School, Minneapolis

HONORARY DEGREES

1980	Honorary Doctorate, University of Athens
1981	Honorary Doctor of Science Degree, Gustavus Adolphus College, St. Peter, Minnesota
1983	Honorary Doctor of Humane Letters, California Lutheran College, Thousand Oaks
1987	Honorary Fellowship in the Royal College of Surgeons of England
1990	Honorary Professor, De Cirugia del Hospital Doce de Octubre, University of Madrid, Madrid, Spain

VISITING PROFESSORSHIPS

1967	Winnipeg General Hospital, Winnipeg,Canada
1968	Johns Hopkins University, Baltimore, Maryland
1969	Marquette School of Medicine, Milwaukee, Wisconsin
1969	Ohio State University, Columbus, Ohio
1969	University of California, Los Angeles
1969	Massachusetts General Hospital, Boston
1970	Rochester School of Medicine, Rochester, New York
1970	Harvard University Medical School, Boston, Massachusetts
1970	Balfour Visiting Professor of Surgery, Mayo Clinic, Rochester, Minnesota
1971	St. Mary's Hospital and Medical Center, San Francisco, California
1973	University of Cincinnati Medical Center, Cincinnati, Ohio
1975	University of Arkansas, Little Rock
1975	Wayne State University, Detroit, Michigan
1975	Memorial Hospital for Cancer and Allied Diseases, New York City
1979	University of California, San Diego, School of Medicine
1979	Rives Visiting Professor, New Orleans, Louisiana
1980	Renee Tanger-Lowenberg Memorial Foundation Lectureship, Atlanta, Georgia
1980	New York University Medical Center, New York City
1980	Milton S. Hershey Medical Center, Pennsylvania State University, Hershey
1981	Mercy Hospital and Medical Center, Metropolitan Group Hospitals, Abraham Lincoln School of Medicine and University of Illinois, Chicago
1981	State University of New York at Stony Brook
1982	College of Physicians and Surgeons, Columbia University, New York City
1983	University of Manitoba, Winnipeg, Canada

1984	Benjamin Park Visiting Professor and Lecturer, New York Hospital-Cornell Medical Center, New York City
1985	Gothenburg University, Gothenburg, Sweden
1985	University of Iowa, Iowa City
1986	Brown University, Providence, Rhode Island
1986	Mt. Sinai Medical Center, New York City
1987	North Dakota Orator, North Dakota Medical Society, Grand Forks
1987	Long Island Jewish Medical Center, New Hyde Park, New York
1989	College of Physicians and Surgeons, New York City
1990	University of Cincinnati, Cincinnati, Ohio
1991	Baylor University Medical Center, Dallas, Texas
1991	Harvard Medical School, Boston, Massachusetts

NAMED LECTURES

1968	William C. Beaumont Memorial Lecturer, Wisconsin Medical Society
1969	Sommer Memorial Lecturer
1973	Twenty-Fourth Annual Strauss Lecturer
1975	Masauki Hara Lecturer, University of Arkansas
1978	Morita Day Memorial Lecturer, William Beaumont Hospital, Royal Oak, Michigan
1982	McGraw Lecturer, Joint Meeting of Detroit Surgical Association and Academy of Surgery, Detroit, Michigan
1982	Reinhoff Lecturer, Johns Hopkins Hospital, Baltimore, Maryland
1984	William C. Beaumont Memorial Lecturer, Wayne County Medical Society, Detroit, Michigan
1985	R. Tait McKenzie Lecturer, University of Wisconsin, Madison
1985	Hale-McMillan Lecturer, Meharry Medical College, Nashville, Tennessee
1985	18th Annual E.C. James Memorial Lecturer in Surgery, Hamilton Academy of Medicine, Hamilton, Ontario
1985	Second Gelin Memorial Lecturer on Transplantation, Gothenburg University, Gothenburg, Sweden
1986	Willard E. Goodwin Address, Harbor-UCLA Medical Center Los Angeles, California
1987	Samuel L. Kountz Lecturer, Brooklyn Surgical Society
1987	Edward R. Woodward Visiting Professor, University of Florida, Gainesville
1987	Leon Ginzburg Lecturer, Beth Israel Medical Center, New York City

1987	Max Broedel Lecturer, Association of Medical Illustrators, Minneapolis, Minnesota
1987	A.J. Grace Memorial Lecturer, Southwestern Ontario Surgical Society, London, Canada
1988	1988 J.W. Johnson Lecturer, Scripps Memorial Hospitals, La Jolla, California
1989	Mark Allam Lecturer, American College of Veterinary Surgeons, Reno, Nevada
1989	C.Y. Thomas, Jr., Lecturer, Midwest Organ Bank Transplant Symposium, Kansas City, Kansas
1989	Walter Estell Lee Lecturer, Graduate Hospital, Philadelphia, Pennsylvania
1989	David W. Yandell Lecturer, University of Louisville, Kentucky
1989	Walter Estell Lee Lecturer, Graduate Hospital, Philadelphia, Pennsylvania
1990	John H. Trescher Lecturer, Milton S. Hershey Medical Center, Hershey, Pennsylvania
1991	60th William J. Mayo Lecturer, University of Michigan Ann Arbor
1991	Francis D. Moore, Jr., Lecturer, Harvard University, Brigham and Women's Hospital, Boston, Massachusetts

PROFESSIONAL SOCIETIES

American Association for the Advancement of Science
American Association for Laboratory Animal Science
American Association of Immunologists
American Board of Surgery
    Diplomat
    1982-88 Member of Board
    1985-86 In-Training Examination Committee
    1985-86 Committee on Credentials
American College of Angiology
1983 Honorary Member
Fellow, American College of Surgeons
American Diabetes Association
American Heart Association
American Medical Association
American Society for Experimental Pathology

- American Society of Nephrology
  - 1972 Council Member
  - 1977-78 President
  - 1980-88 Chairman, Education Committee
  - 1987 Member, Advisory Committee on Issues
- American Surgical Association
  - 1984- Committee on Honorary Fellowships
  - 1988-89 President
  - 1989-92 Council
  - 1989-90 Committee on Ethics
- 1969 President, Association for Academic Surgery
- Central Surgical Association
- 1981 Honorary Member, Columbia Society of Nephrology
- Council on the Kidney in Cardiovascular Disease
- Hagfish Society (Immunology)
- Halsted Society
- Hennepin County Medical Society
- Howard C. Naffziger Surgical Society
- Correspondent Member, Italian Surgical Research Society
- International Society of Nephrology
- International Society of Surgery
- Kansas City Surgical Society
- Minneapolis Surgical Society
- Minnesota Academy of Medicine
- Minnesota Medical Association
- Minnesota State Medical Society
- Minnesota Surgical Society
- 1988 Founding Member, The Pan-American Society for Dialysis and Transplantation
- Portland Surgical Society
- St. Paul Surgical Society
- Sigma Xi
- Society for Experimental Biology and Medicine
- Society of Clinical Surgery
- Society of Surgical Chairman
- Society of University Surgeons
- Surgical Biology Club
- Transplantation Society
  - 1971-82 Council Member
  - 1984-86 Vice President (Western Hemisphere)
- 1990- Honorary Member, The Tulane Surgical Society

AWARDS

1952	Alpha Omega Alpha
1962	California Trudeau Society Award
1964-69	Markle Scholar of Academic Medicine
1967	Football Alumnus of the Year, University of California, Berkeley
1974	Alumnus of the Year, University of California, Berkeley
1977	Alumnus of the Year, University of California, San Francisco, School of Medicine
1978	Annual Brotherhood Award, National Conference of Christians and Jews
1978	Award for Distinguished Achievement, Modern Medicine
1979	Walter A. Gordon Distinguished Citizen-Athlete Award
1982	International Great American Award, B'nai B'rith Foundation
1983	Kabakjian Award
1983	Man of the Year, WCCO Radio, Minneapolis
1984	Distinguished Alumnus of the Year, Oakland High School
1985	Golden Key National Honor Society, University of Minnesota
1985	Distinguished Minnesotan Award, Bemidji State University, Bemidji, Minnesota
1985	Uncommon Citizen Award Greater Minneapolis Chamber of Commerce, Minneapolis
1985	Regents' Professor, University of Minnesota
1986	1986 FDR Memorial Award, March of Dimes
1986	Man of the Year Award, Armenian Professional Society
1986	Honorary Membership, Minnesota Chapter of Mortar Board
1986	Outstanding Minnesotan Award, Minnesota Broadcasting Association
1986	Jay Phillips Distinguished Chair in Surgery, University of Minnesota
1987	Honorary Fellowship in the Royal College of Surgeons of England
1987	Sir James Carreras Award, Variety Clubs International

EDITORIAL POSTS

1967-	American Journal of Surgery (Associate Editor, 1982-)
1968-	Journal of Surgical Oncology
1968-	Journal of Surgical Research
1968-	Minnesota Medicine
1970-	Transplantation
1970-	Transplantation Proceedings, Board of Clinical Editors 1981-84
1970-85	Yearbook of Surgery
1971-	Surgery (Associate Editor, 1971-)
1972-	Annals of Surgery

1973-	Surgical Techniques Illustrated
1976-	World Journal of Surgery
1980-	American Journal of Nephrology
1981-	Kidney International
1984-	In Health
1985-	Surgery, Gynecology and Obstetrics
1986-	Clinical Transplantation (Editor-in-Chief, 1986-)
1986-	Hippocrates
1990-	Journal of Transplant Coordination (Published by the North American Transplant Coordinators Organization)

COUNCIL AND ADVISORY COMMITTEE MEMBERSHIPS

	Member, Advisory Committee on Hemodialysis and Renal Transplantation, Department of Public Welfare, Minnesota State Medical Association
	Consultant, Upper Midwest Chapter of the National Kidney Foundation
	Member, Board of Trustees, Minnesota Medical Foundation
	Member, Screening Committee for the Dernham Postdoctoral Fellowships in Oncology (administered by the California Division of the Cancer Society)
	Member, State and Provincial Advisory Committee, American College of Surgeons
1965-69	Special Consultant, United States Public Health Service, National Institutes of Health, Clinical Research Training committee, National Institute of General Medical Sciences
1966-68	Consultant, United States Bureau of the Budget
1968	Member, Scientific Advisory Board, National Kidney Foundation
1970	Member, Committee Regarding Ethical Problems, International Transplantation Society
1970	Member, Legislative Liaison Committee of the National Kidney Foundation
1970	Member, Surgical Study Section A, Division of Research Grants, National Institutes of Health
1970	Member, Scientific Advisory Committee of the National Council on Tissue Utilization and Transplantation
1971	Chairman, Renal Transplant Advisory Group, Veterans Administration Hospital
1971-78	Member, Board of Scientific Consultants, Sloan-Kettering Institute for Cancer Research
1971	Neutral Arbitrator for the National Football League

1973	Member, Honorary Advisory Board, Association of Kidney Patients, Inc.
1978	Board of Directors, Vikings Children's Fund
1985	Chairman, Organ Transplantation Committee, Central Veterans Administration, Washington, D.C.
1985	Board of Directors, Metropolitan Boys Choir of the Twin Cities
1985	Board of Scientific Advisors, Farmacon Research Corporation
1986	Blue Ribbon Advisory Council, Campaign for Child Survival
1986	Consultant to Bureau of Standard Development in Health Care for New York State
1987	Honorary President, Commission for Research and Organ Transplants, Ararat International Academy of Surgeons
1987	Honorary Council, National Conference on Christians and Jews
1989	Honorary Chairman, Camp Confidence Classic Tennis Tournament
1989	Honorary Chairman, Multiple Sclerosis Society's Bachelor Classic III
1990	Scientific Consultant, Cetus Corporation, Emeryville, California
1990	Member, International Scientific Congress Committee, Society for Organ Sharing
1990	Chairman, Community Consortium Clinic, St. Paul, Minnesota

PUBLICATIONS

Includes over 1,100 articles and several books in all areas of transplantation (diabetic transplantation, organ preservation, rejection, liver, kidney and pancreas transplantation, and immunosuppression)

A THEORETICAL AND EXPERIMENTAL APPROACH TO TRANSPLANTATION: THE DUKE EXPERIENCE

D. Bernard Amos

Address: Division of Immunology
Duke University Medical Center
Durham, North Carolina 27710

D. Bernard Amos

1960

1985

A THEORETICAL AND EXPERIMENTAL APPROACH TO TRANSPLANTATION: THE DUKE EXPERIENCE

D. Bernard Amos

The first paper on human transplantation antigens from our laboratory at Duke University began, "White cells undoubtedly carry many transplantation antigens. An analysis of the isoantigens of white cells can provide information about the transplantation antigens of other tissues, and has great potential value in genetic studies on linkage" (1). We could never have guessed just what a wealth of genetic information and what new insights into genetic regulation and diversity would emerge, or even that these were some of the early studies that would define the MHC and open up an explanation of its rich and diverse functions. This is a personal reprise of the early studies on transplantation immunogenetics from the laboratories at Duke University, with some digressions into other events that shaped transplantation research in our laboratory and also throughout the world.

My own interest, which was initially secondary to an interest in immunity to tumors, dates back to my entry into the laboratory of Dr. Peter Gorer in 1951. Since no monograph on the history of transplantation would be complete without reference to the two Peters, Peter Gorer and Peter Medawar, it is appropriate to touch on their work and on the interplay between them.

Peter Gorer lived long after the great age of philosopher-scientists but he had the broad range of curiosity of a natural philosopher. He owed a great deal to his early contacts with J. B. S. Haldane and Ashley Miles. He was drawn into immunogenetics by a furious controversy that was raging over a form of immunotherapy for cancer. In a long series of papers, Thomas Lumsden reported on the astonishing regressions obtained by treating cancer-bearing rats with immune serum, claims that were disputed by another cancer biologist, Ludford. At issue was the true tumor specificity of the serum, a controversy that has erupted at other times, but on this occasion, apparently the two protagonists were well matched and unyielding in their stance. The question was a very important one and Lumsden was widely quoted. A report from one of his former associates, Phelps (2), that the cytotoxic effect could be removed by absorption with spleen and therefore was against normal tissue antigens did not discomfort Lumsden, who continued to publish (3). Gorer realized that the only way to resolve the question, and indeed the only way to find out if tumor antigens were recognized by xenoantibodies, was to define normal tissue antigens and then to determine which, if any, antigens were peculiar to the tumor. This could only be done by working with mice since inbred strains of mice, but not of rats, were available. Haldane brought C57Bl mice from the United States and three other strains were obtained locally.

Gorer had demonstrated alloantigenic differences between some of the four available inbred mouse strains before I joined him in 1951. He, along with Sally Allen and George Snell, published their monumental discovery of H-2 (4), but he was having difficulties detecting the antigen of some strains, especially the C57 Blacks. Antisera raised in Blacks against A strain tumor were detectable as hemagglutinins (5) but the reciprocal was not true. A strain serum would not agglutinate cells from the Blacks even though the animals were obviously immune since they rejected EL4, a tumor induced in the Blacks. He was attempting other procedures for detecting what were regarded as incomplete antibodies including a Coombs test, and I was asked to work out another type of detection system. After about a year of considerable frustration, I managed to devise a fairly reproducible system for agglutinating BCG-induced peritoneal exudate cells (6). After that, Gorer and I did a number of things together. One of my own triumphs was to protect C57 mice against their syngeneic tumor EL4. Peter doubted it could be done but I went ahead anyway and injected 0.5 ml of hyperimmune alloantibody and then gave a lethal dose of tumor. To my delight the mice lived. Peter, still doubting said, "Try it with 10 times the amount of tumor and cut down the dose of antibody." Angry with this excessive caution, I did as I was told, and made a believer out of both of us (7). We could, and did, explore this novel form of immunity under the very stringent conditions he imposed and eventually reported on the X antigen of EL4. This was probably the first report of a tumor-specific antigen. Another triumph was the recognition of three intra-H-2 recombinants (8).

Peter Gorer was, as I have said, a skeptic. Peter Medawar was another. Medawar knew of Gorer's demonstration of hemagglutinins in mice so he tried looking for similar antibodies in his own system, namely skin graft rejection in rabbits. He found nothing. Medawar thus became very doubtful about the value of hemagglutinins and suggested at one point that there were three different antigens which he called T, H, and E (9). T was for transplant antigens, H for hemagglutinating antigens, and E for the enhancing antigens Snell, Kaliss, and their colleagues were working on. According to this scheme, the H antigens were nonfunctional. It struck me as absurd to suppose there could be three loci with such an extraordinary degree of polymorphism.

At a meeting between the two Peters that also included Rupert Billingham, Elizabeth Sparrow, Leslie Brent, and me, we agreed on two things - that the pub we were meeting in was a very fine one, and that we should do this more often. We also agreed that we should combine forces to resolve the T and H antigen issue for skin grafts. Medawar's team had experience in skin grafting, which we did not, and Gorer and I had greater experience in serology. Billingham and his colleagues grafted the mice, Gorer and Mikulska (his technician) tested for hemagglutinins and I tested for leukoagglutinins. We found reasonable but not high titers of antibodies (10). Medawar was not completely satisfied and at another pub lunch suggested that we try the reciprocal experiment, namely, to immunize against a pure suspension of red cells. His team would then test for second-set rejection. This experiment was never done because Gorer and I couldn't get antibody titers to go higher than 1/32 and because we couldn't be certain, as Medawar insisted, that our red-cell suspension was free from lymphocytes.

After leaving Gorer to join Ted Hauschka in Buffalo (for a 1-year fellowship that stretched out for 7 eventful years), my life centered around the antigenicity of tumors. We discovered several different X antigens that seemed to be tumor specific (11), we also showed that the levels of H-2 had a relationship to the ability of tumors to cross strain barriers (12), and also documented a rich variety of antigens that were shared by tumors and tissues (13). Parenthetically I'd like to say a word about terminology. We initially identified new (non-H-2) antigens by Greek letters, α, β, γ, etc., a practice followed by Reif and Allen who designated a thymic antigen theta, later Thy 1. When we were pretty certain of the characteristics of two of these, α and β, we named them H-5 and H-6 (14), since H-1 and H-4 had already been named. The mouse nomenclature committee later renamed them Ea-5 and 6. Our "H" was disallowed because H-5 and H-6 had not been shown to be transplantation antigens. They were renamed Ea because they were on red cells. This seemed evocative of the attempted categorization by Medawar of T and H antigens. The change seemed inappropriate because we'd originally identified them on leukocytes and tumor cells. H-5 and H-6 also had a very specific distribution on kidney and other tissues. The designations would be different now because they would surely be called CD which is less evocative.

While in Buffalo I began to study the mechanisms of graft rejection using ascites tumor cells as targets starting with the hypothesis that antibody was responsible for certain aspects of graft rejection. There were, at the time, two fundamentally different viewpoints about the mechanism of allograft destruction (and the controversy has not yet been resolved). Medawar, Brent, Mitchison, and their colleagues believed that graft destruction was through a cellular process indistinguishable from delayed hypersensitivity (15). Their hypothesis was supported by their ability to transfer immunity with cells and not with serum, the effectiveness of draining versus contralateral lymph nodes, the histologic appearance of rejecting grafts, and by their inability to demonstrate antibodies after graft rejection.

Gorer and I thought that antibodies were important because we could transfer immunity to some tumors with serum and because we could reproducibly demonstrate antibodies after tumor or skin graft rejection. Glen Algire with his colleagues, Weaver and Prehn, in a series of three provocative papers, thought they had finally settled the issue through their expert use of diffusion chambers to isolate the transplant from the host (16-18). Grafts inside a porous chamber that would admit cells would be rejected; grafts in cell-impervious chambers survived unless immune cells were put directly into the chamber. They thought this was conclusive proof of the involvement of cells and not antibody; Gorer was not so sure for several reasons, one being that antibody levels in the cell-impenetrable chambers would be very low since the mice were not hyperimmunized.

One of Algire's favorite targets was Harderian gland from the orbital region, a tissue not usually used in transplant studies. We did not know how much the choice of target had influenced the result so June Wakefield and I began by studying the growth of different tumors in diffusion chambers (19). We then passively immunized the hosts with antibody. Although sensitivity varied greatly from tumor to tumor, growth was generally inhibited if antibody titers were high and growth inhibition persisted as long as the antibody levels were maintained (20). Interestingly, target lysis was greatly augmented if fresh guinea pig or mouse serum as a complement source was injected into the peritoneal cavity; evidently complement levels were critical (21). The role of complement had not been considered previously; it is still usually overlooked, although several of the early components of complement are produced by graft-infiltrating cells. It was also noteworthy that mouse complement was as potent as guinea pig complement in vivo even though it was very feebly lytic in vitro.

In 1961 I was invited to Duke to help establish the genetic basis for a new kidney transplant program. The first necessity was to set up a test system for detecting tissue antigens. As noted in the introductory paragraph, white cells were the targets and leukoagglutination was chosen as the test. This was partly because leukoagglutination had picked up all the H-2 antigens detectable by hemagglutination (as well as other antigens of the mouse not found on red cells), and partly because van Rood had used leukoagglutination successfully to detect the 4a and 4b leukocyte and tissue antigens in man (22).

Once we had established a reliable serologic method (1) we could build up a battery of sera and accumulate a typed panel. Our detection procedure had several advantages over published methods. We

Peter Gorer

Jon van Rood

Jon van Rood Paul Terasaki

used EDTA as anticoagulant and thus avoided problems of complement participation, we eliminated most of the platelets by differential centrifugation and so the test was easier to read, and, in siliconized glassware, the suspension was less liable to clump spontaneously. It was also a semimicro method that could be set up using 20 or 25 μl of serum, and it showed a feature not described, to my knowledge, by others. While most sera agglutinated only leukocytes, others gave mixed clumps in which red and white cells were interspersed. Using this test we screened pregnancy sera obtained just before or shortly after delivery; 20/34 Black sera (58.5%) and 15/20 sera from Whites (75%) were positive. This compared with only 20.4% positive sera from multiparous or transfused blood bank donors, approximately the proportion reported by other laboratories. Although this procedure was as good or better than any other agglutination procedure published, it was far from ideal. Cells could not be stored, even for a day, and occasionally we would lose all cells if the reagents were slightly "off" (they went "stringy" and were unusable). We attempted cytotoxicity but those complement sources we tried were not promising. Our rabbit serum appears to have been toxic, as was dog. Sheep gave very low titers and guinea pig was inactive, so we were glad when Walford (23) and Terasaki (24) reported success with rabbit serum. Rabbits raised at home by one of our technicians gave us better complement than the vivarium-raised animals we had originally tried and we happily converted to cytotoxicity. We later introduced a wash step to reduce false negative (CNAP) effects (25). One can tell at a glance if a laboratory is using this modified procedure; there is always a large blue stained trash can which is used to flick off excess trypan blue, in the center of the laboratory. Trypan blue gives a color which is easier to read than eosin but the cells do not take up stain properly if there is serum in the suspending medium, hence the "flick."

Having good test procedures and a laboriously collected battery of sera we joined van Rood, Dausset, Payne, Walford and others in charting the complex interrelationships of the antigens.

Although most of our initial efforts were directed at improving our ability to define antigens serologically, we also compared the antigens so defined with functional assays. Before 1967, the most widely used were the normal lymphocyte transfer test (NLT) of Brent and Medawar (26) as adapted to man by Gray and Russell (27) and the third man skin graft procedure of Rapaport, et al (28). In the NLT live lymphocytes were injected intradermally. Positive reactions were characterized by erythema and induration appearing at 24 to 72 hours. Records could be made permanent by tracing the outline of the lesion with a ballpoint pen and then transferring the ink to a strip of selotape which was then stored on the subject's record card. Some other features of the test are mentioned below.

The 1962 to 1965 period saw a marked evolution in our ability to define antibodies. At first we were dependent upon gifts of small quantities of serum from colleagues. Since all tests had to be done at least in duplicate and each determination took 20 to 25 μl of serum (semimicro procedure) only about 18 patients or panel donors could be typed on a precious 1 ml of serum. Shared sera from other laboratories were at first augmented by blood from transfused or multiparous donors. As we carried out the NLT tests, however, we found these subjects could provide an excellent supply of novel antibodies. This was an accidental finding resulting from our desire to ascertain the reproducibility of the NLT.

For the NLT we found about 5 million lymphocytes per intradermal site gave convenient reactions of about 8 mm induration and erythema after 48 hours (29). When

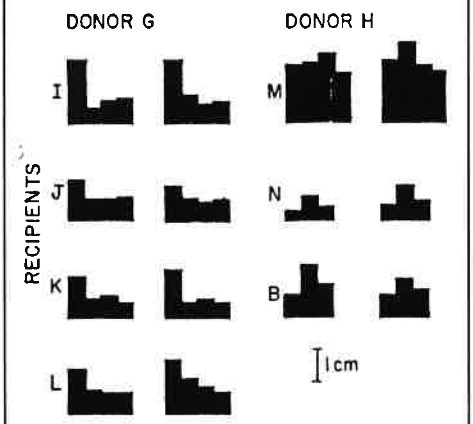


Figure 1. Comparison of the inflammatory response in six normal (I to N) and one immune (B) subject receiving duplicate injections of 5x106 lymphocytes from one of two donors. (Erythema measured at successive 24 hourly intervals). (ref 29)

we repeated the determinations on the same subjects several weeks later, we hoped for the same ranking of reactivity from the same donor panel although we half expected a more vigorous and larger reaction if the recipient had become immune. In fact, we were puzzled to find smaller responses in many subjects. Serum samples were tested and cytotoxic antibodies were found; there was an excellent correlation between reduced reactivity and antibody production. This was useful for our serologic work but bad for our NLT test since its reproducibility could never be measured.

Skin grafting was also compared with serology in unrelated subjects. Volunteers were typed with all available sera (usually about 30) and arranged in groups of four (30). Two pairs A and B, C and D were phenotypically similar or "compatible." A and C, B, and D were phenotypically distinct, "incompatible." Reciprocal 11 mm skin grafts were exchanged between A and B, and A and C, also between C and D, D and B. Unfortunately there was no correlation between phenotypic similarity (compatibility) and graft rejection time. The conclusion was that there were other antigens distinguishing A from B or C from D which we could not detect, so these subjects were recruited into our antibody procurement schedule and further immunized intradermally; about half of them gave useful antibodies. The sera were used to phenotype transplant donors and recipients both for our own panel and then for the much larger panel of subjects in the South East Organ Procurement Foundation program (SEOPF). I will now digress a little to speak about collaborative efforts including SEOPF, the serum bank of the NIH collaborative program, and the workshops.

SEOPF, which will be described later, stemmed from an impetus given by one of the Public Health Service Agencies (HCFA) in a program fostered by the Director, Dr. Frederick L. Stone. Like many other transplant programs, it also benefited from the support of the Transplantation and Immunology (TI) program of the National Institute of Allergy and Infectious Diseases headed by John Overman and later by Donald Kayhoe. The advisory committee for the collaborative program was an unusual one. NIH guidelines forbade the use of members of study sections on other NIH committees, so we had to recruit transplant immunologists who were not already consultants. Many of the members, including myself, had not served on a study section and we had to work out our goals and our rules of procedure as we went along. Al Stetson, chairman of Pathology at NYU, was an admirable vice-chairman in this effort. In our first year of operation we had a budget of $200,000. Top priority was given to building a serum bank. We gave contracts of $30-35,000 to laboratories with existing procedures for serum procurement with the understanding that this money would serve as a supplement to encourage contractors to increase the yield of antibodies and to deposit the surplus with the bank. Dausset, Ceppellini and van Rood were included in our list of contractors and a separate contract was awarded to Flow Laboratories to provide frozen storage, and later, lyophilization services. In addition, we allowed $2.50/ml for donations by other investigators. Serum donor laboratories were given top priority for withdrawals of bank sera. A number of reagent quality sera were obtained and distributed in this way. The sera became extremely well characterized because the established users were required to report their results to the bank.

One other feature of the contract program was the annual contractors meeting. Each contractor gave a progress report, there was a report on the state of the bank, and future policy was discussed. During one particularly important meeting held in Williamsburg in 1967 (31), the terminology of HLA was debated, the designation HL-A was formally agreed upon, and the first HL-A antigens were defined. There was, of course, no recognition of the first and second loci alleles and the antigens were numbered consecutively, more or less in order of their discovery. (A weakness of committees is that they promulgate those decisions the majority agree upon even if individuals disagree.) In retrospect, we could have made provision for an A (first series) and a B (second series) right from the start and saved a lot of confusion in terminology later, but we were so happy to have agreed upon a name for the main system that other decisions seemed inconsequential. The collaborative program also held teaching workshops and published catalogs listing hundreds of sera.

SEOPF came into being because of the relationship that grew up between transplant surgeons and immunologists at the Medical College of Virginia (MCV), Johns Hopkins University, Duke, the University of Maryland, the University of Virginia (UVA) and Emory University. Some leading proponents were David Hume and his colleagues from MCV, H. M. Lee and Mel Williams, Les Rudolf from UVA, Del Stickel, H. F. (Sig) Siegler, Frances Ward and myself from Duke, and Norman Ende from Emory (32). Norman Ende was an unusual participant. As a pathologist he provided an excellent supply of organs even though Emory was not a very active transplant center. HCFA contracted to pay 100% of organ procurement costs for the first year, 66% for year 2, 33% for year 3 and thereafter all costs were to be generated by the program itself. The costs included HLA typing as well as organ procurement and transportation.

SEOPF and the exchange registry founded by Paul Terasaki were contemporaneous programs funded by the same agency but operating in rather different ways. The Terasaki program was originally more all embracing and many centers participated. SEOPF was more restricted and had rather stringent requirements for admission. All SEOPF centers used the same serum panel for typing donors and recipients and conducted a series of workshops to minimize variations in procedures between laboratories (33). Standardization in the techniques for harvesting organs was later adopted and there was considerable exchange of information between the centers concerning perfusion, transportation, etc. Donor/recipient matching was coordinated through a computer program set up by Frances Ward. As computer matching grew more sophisticated, SEOPF could increase the number of centers participating and eventually, nurtured by our then programmer, Leon Hudgins, it spawned the United Network for Organ Sharing (UNOS) that is now the paramount organization in the United States.

The Histocompatibility Testing Workshops arose from a different organization, the Transplantation Committee of the National Research Council--National Academy

Jean Dausset

Fleming Kissmeyer-Nielsen *Jean Dausset* of Sciences. Its genesis has been described elsewhere (34). From 1964 it provided an active focus for collaborative research and also served as a training center and means of quality control for new laboratories.

The Transplantation Society arose indirectly from the Histocompatibility Testing Workshops. In the 1960s, the principal means of communication between transplant scientists was the series of meetings organized by John M. Converse and Blair O. Rodgers through the New York Academy of Sciences. These admirable meetings attracted an even larger audience. Although the meetings helped the field to advance, there was a sense that some form of professional organization dedicated to transplantation and immunogenetics was needed. There had been previous attempts to found such societies. In the United States, Ben Rasmussen, Clyde Stormont, Ray Owen, Carl Cohen, and others had led two exploratory discussions with the objective of forming The American Immunogenetics Society; and in Europe Jacques Mathé and Dirk van Bekkum had also held discussions with their colleagues aimed at forming a transplant society, but nothing tangible followed any of these meetings. The Histocompatibility Testing Workshops had, by the time of the second meeting in Leiden, begun to assume some continuity of pattern and could conceivably form the framework for a society, but the participants of the workshops were reluctant to assume the restrictions inherent in any formal society and continued with their loose organization which had no written constitution or financial standing. Informal talks about starting an international society were held and it was decided to ask someone from outside continental Europe to act as an organizer. Leslie Brent and I were regarded as suitably disinterested parties. Leslie's demurral came with extreme rapidity; he was moving his laboratory from London to Southampton and had no free time, so, by default, I became chairman of the steering committee for the Transplantation Society.

The preliminary meeting was held in an art museum near Leiden in conjunction with the 1965 Histocompatibility Testing meeting. The principal agenda item was whether or not to go ahead with the formation of the International Transplantation Society or whether to amalgamate with a Hematological Society. It was felt that the needs of transplantation were distant from those of the blood groupers, and an independent society was decided upon. The word "International" was quickly dropped because of informal advice that the N.I.H. was not anxious to support any more International societies and, thereafter, it became known simply as the Transplantation Society. I don't remember if the vote taken at the organizational meeting was unanimous but it was very positive and provided a strong mandate so I asked several colleagues to help develop a framework for the new society and to suggest others who should be invited. Jerry Lawrence was chairman of the constitutional committee, Felix Rapaport was secretary of the steering committee and George Klein headed the nominating committee. We hammered out a constitution which was put to a membership that was hastily elected during the Seventh Transplantation Conference of the New York Academy of Sciences. Peter Medawar, who had not been greatly involved in the early formative stages of the Society, was a unanimous choice for the first President. Jean Dausset asked if I would accept the title of Founder President; this title was later changed to Past President and to the amusement of Ceppellini and others, I was duly elected. Felix Rapaport and Hans Balner as long-term secretaries did much to mold the growing society, and the society's publications, especially *Transplantation Proceedings*, added greatly to its prestige.

To return to our own research program in transplantation. The transplant team at Duke (later the Duke-Durham Veterans Administration team) was initially led by a transplant surgeon, Delford Stickel; a urologist, Jim Glenn; a nephrologist, R. R. (Ike) Robinson; and an immunologist, myself. For years our leading nurses were Norma Harris and Fran Ross and our technicians were led by Marilyn MacQueen. Our first kidney transplant was performed in 1965 (35). This was one of the first cases in which donor selection was based on histocompatibility. The donor chosen was one of seven siblings.

Matching was based on cytotoxicity (36), agglutination (1), lymphocyte transformation in vitro of Bain, et al (37) and the third man test of Rapaport, et al (28). Four of the siblings were excluded because of antigenic incompatibility. The patient, JS, required less than 200 mg azathioprine and 15 mg of prednisone for maintenance and the transplant served him perfectly for over 20 years before being replaced. For those who never saw one of the nephritic early transplant recipients, I'd like to comment that these patients were almost moribund when transplanted, they were pallid with anemia and were prostrated with extreme weakness. Three months or so after the transplant, I was surprised to be greeted in the corridor one day by a bronzed and robust-looking man who obviously knew me very well. I didn't recognize him until he told me he was JS. Another of our patients, WB, who received a very early genotyped kidney from his sister, helped us in many ways. A lay Baptist minister, he introduced us to other ministers who in turn educated their congregations. He also helped us convince the local morticians about the benefits of transplantation. Education of physicians, legislators, and certain segments of the public was an important activity if transplantation was to become widely accepted. WB and other patients were valued witnesses before the Gottschalk Committee of the Bureau of the Budget investigating the treatment of end-stage renal disease. Another patient agreed to be presented by H. F. Seigler to an immunology class. Sig showed a cushingoid patient and pointed out the tell-tale signs of steroid therapy. He then showed our transplant recipient and asked the students for a diagnosis. When one ventured to say it was apparent he had steroids, Sig asked, "Why?" The student pointed out the abdominal obesity whereupon the patient said, "Milwaukee muscle" and laughed. He and several of our early recipients of HLA-identical kidneys received only azathioprine for maintenance and received no steroids. One of our favorite recipients (VH) developed a surgical infection and all immunosuppression was discontinued; we felt

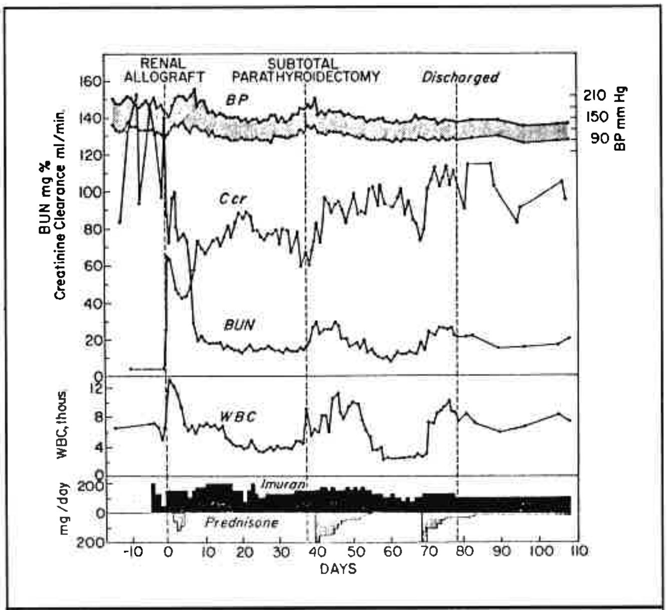


Figure 2. (ref 35)

it necessary to let the kidney go to save her from the infection. To our delight she recovered and did not reject the graft. At my urging, immunosuppression was not restarted and the kidney functioned perfectly for over two years. VH developed acute rejection after a mild respiratory infection and we never tried zero immunosuppression in other patients. Awasaki has summarized the findings in a number of such cases (38).

Phenotypic matching was obviously advantageous in families but was much less successful in unrelated pairs. In 1965, when JS received his kidney, we did not really know what we were matching for. Chester Zmijewski's and my main concern was to identify the antigens and define their relationship to one another (39,40). Progress would probably have been more rapid if we had combined serology with the NLT in families, but we had misgivings about transferring lymphocytes in hospital-families so we combined serology with the third man skin graft test and later, with MLC testing. Dausset's 1965 hypothesis, that the antigens he and his colleagues could detect all belonged to one immensely polymorphic system (41), was only a hypothesis and we did not, at that time, see simple segregation patterns in families to provide genetic support for his idea. Typical of the early families, skin grafts were exchanged between a patient, R, and his siblings. R, being a potential kidney recipient, could not receive a graft for fear of sensitization but could donate to 4 sibs who also exchanged skin with each other. Antigens were detected by agglutination and cytotoxicity and scored as the number of incompatibilities detected. In today's terms, the panel included two HLA-identical pairs rejecting each other's skin in 26, 20, 24, and 27 days and two-haploidentical pairs rejecting in 13 to 16 days while R, unfortunately, was haploidentical to both pairs (42). The sera were still unknown and even the HLA-identical grafts scored a few incompatibilities; of course, the haploidentical grafts scored more. Even with this crude form of serotyping we were very successful in predicting compatibility. Of our first six patients, the five who were judged most compatible had functioning grafts seven months or more after transplant and three never required steroids (43).

It is not surprising that we found it difficult to deduce the genetic relationships between antigens. Not only were the sera unselected but we were using two different serological procedures that gave answers that were sometimes similar and sometimes different (44). Some of the problems were discussed by Zmijewski and Amos (39), in which we said of cytotoxicity, "Antibodies detected by this method are not necessarily the same as those that participate in leukocyte agglutination," and illustrated this by giving reactions of our first transplant patient, JS. This paper also compared MLC and inhibition of mixed agglutination.

Because of the pressures to select donors for transplantation, transplant immunologists subsequently have neglected the other (I nearly said, "minor") antigens. Mixed agglutination using antibody-coated lymphocytes as one of the test cells is an exceptionally sensitive assay that detects unknown antigens and direct binding assays can also reveal new antigens. Minor histocompatibility antigens have been shamefully neglected but in 1966 it was inevitable that they would be dropped since they served to confuse our main purpose which was to assess the simplest aspects of donor compatibility.

A collaboration that developed between Fritz Bach and myself in the mid-1960s was mutually beneficial in understanding the functions of the MHC. Skin grafting and serotyping were well advanced at Duke and mixed lymphocyte culture reactions and access to numerous large families were available at the University of Wisconsin. At first begun as a means of enriching our own experience, the collaboration soon became

Norma Harris *Bernard Amos* *Anna Tiiliakainen*

Bo Dupont *Fleming Kissmeyer-Nielsen* *Edmund Yunis* very exciting. Sharon Lancaster and Karen Sullivan went from Durham to Madison and typed 10 of Dr. Fritz Bach's families. One, the SA family, gave exceptionally simple reactions since none of our sera reacted with cells from the mother, hence we could not fail to see the segregation of the two paternal haplotypes (45). These two segregation patterns also included representatives of several of our serum "groups," showing that there was linkage between antigens. This linkage was further analyzed in other families (46) and then in a collaborative paper in which Bach and I established that the main system, Hu-1 (now known as HLA) controlled MLC reactivity, leukocyte antigens, and skin graft reactivity (47). In this paper, Fritz and I also projected a single locus with at least 15 alleles.

Ceppellini thought the results were too perfect and was mistrustful. He suggested a double-blind test in which Bach and his colleagues would perform MLC tests, my colleagues and I would serotype coded cells, and Ceppellini would receive and correlate results from both laboratories. The correlation turned out to be perfect and Ceppellini's laboratory joined in a three-part study with Duke and Madison (48). In this paper we found that the degree of stimulation was related to the difference in the number of haplotypes shared. We also reported on an exceptional stimulation between a pair of HLA-identical sibs. Two explanations were suggested: stimulation by non MHC antigens, and recombination with an unknown gene within HLA. This anomaly was later picked up in my own and in other families. Mutual stimulation between serologically identical sibs formed the basis for developing our hypothesis that the MLR was a response to incompatibility at a separate locus (49) later designated MLR-S (50) and currently HLA-D. Edmond Yunis and I also postulated a separate locus for delayed hypersensitivity reactions HDR-S (51). The collaboration with Janet Plate, Edmond Yunis and Frances Ward was very exciting. It took some perseverance to get the concept of functional loci accepted. I regret we did not show the same perseverance in pressing our ideas about HDR-S and the grid.

From the time of our ability to detect the segregation of haplotypes, all our families were genotyped. We correlated skin graft rejection with haplotype segregation. In an early paper, Ceppellini had suggested that skin graft survival of greater than 15 days would equate with prolonged kidney graft survival (52); 15 days, in our experience, also seemed to be about the

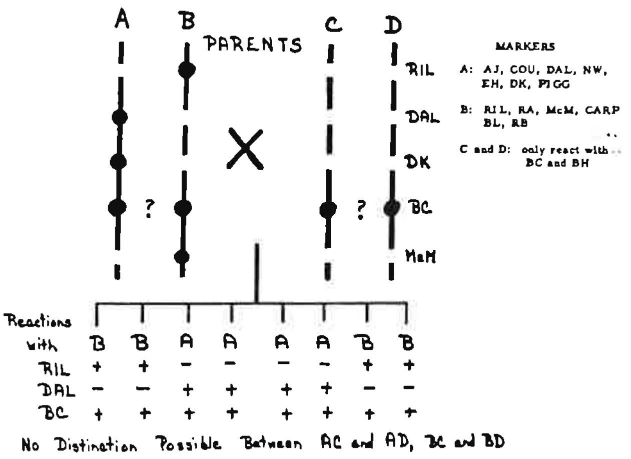

A
B
PARENTS
C
D
X
?
?
RIL
DAL
DK
BC
McM
MARKERS
A: AJ, COU, DAL, NW, EH, DK, PIGG
B: RIL, RA, McM, CARP BL, RB
C and D: only react with BC and BH
Reactions with B B A A A A B B
RIL + + − − − − + +
DAL − − + + + + − −
BC + + + + + + + +
No Distinction Possible Between AC and AD, BC and BD

Figure 3. Schematic diagram of part of the chromosome determining a series of antigenic specificities. "Alleles" A and B are carried by the father, C and D by the mother. The antigenic determinants are inherited as closely linked units. (ref 45)

lower limit of survival for skin exchanged between "compatible" siblings. An analysis of 22 families revealed an inverse relationship "between the number of days the skin grafts survived and the severity of rejection activity within the kidney" (53). This was soon followed by more complete analysis of kidney survival of 26 genotyped families (54) and of the fate of skin grafts in these families (55). These studies firmly established that HLA was the most potent of the human histocompatibility antigens but also showed immense variation in haploidentical pairs. We were unable to tell if a haploidentical graft would be rejected quickly or slowly and the MLR was not helpful in distinguishing between greater or lesser immunogenicity (56). The report that there was no simple correlation between degree of proliferation in MLR and graft survival was greeted with dismay and some disbelief, but, unfortunately, it has been abundantly confirmed. The MLR is a useful indication or confirmation of HLA identity between siblings but is not a prognosticator of graft survival in other combinations.

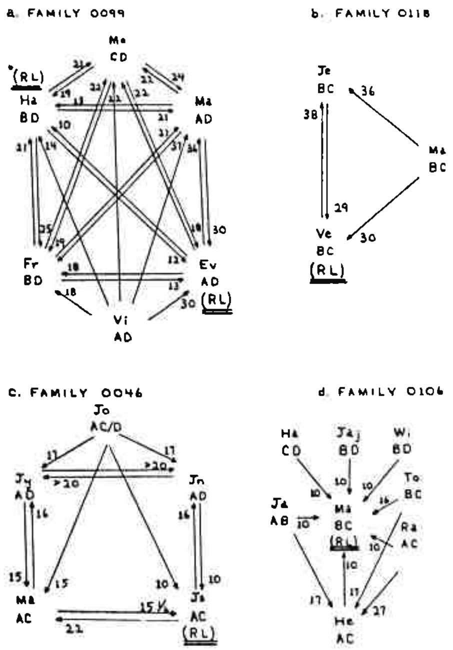


*Figure 4. Skin grafting in 4 families. *(RL) Postulated recognition locus. (ref 57)*

To better understand graft survival we then followed two lines of research: attempts to define recipient reactivity and attempts to define the immunogenicity of the graft. Variation in recipient reactivity was deduced from some of the family skin grafts. In family 0099, for example, the patient (V) gave skin to her mother and to two HLA-identical and to two haploidentical sibs (57). A total of 25 grafts was exchanged in this one family. Of these, six were HLA identical and 19 haploidentical. The mean survival time for HLA-identical grafts was 29.2 days ranging 21 to 36 days and for the haploidentical grafts, 17 days ranging 10 to 24 days. Although differences in HLA antigens between haplotypes and non-HLA antigens could account for some of the variability. One sibling, EV, rejected haploidentical grafts in 14.3 days while her HLA-identical sibling rejected the grafts from the same donors in 22 days, suggesting she was less able to react. Fortunately, this problem is much less pressing now because more powerful immunosuppression eliminates much of the consequence of hyperreactivity, but I still don't know how to evaluate it. To try to resolve the problems of immunogeneity and host reactivity we then developed a mouse model.

By mating four different strains of mice YBR ($H\text{-}2^d$,) DBA1 ($H\text{-}2^q$), C3H ($H\text{-}2^k$), and C57BL ($H\text{-}2^b$) we could make two sorts of F_1, dq, and kb which when intercrossed gave dk, db, qk, and qb (F2) offspring in approximately equal numbers. The distribution of rejection times was roughly similar to the values for human familial grafts with the same dose effect, namely, two-haplotype differences rejected faster than one and H-2 identical persisted longest (58) but non-MHC effects were stronger in mice than in humans. We later repeated the experiment using H-2 congeneic mice to eliminate the cumulative effect of minor antigens. Interestingly, we detected an unexpected contamination or mutation in one of the mouse strains, but in neither series was there any obvious difference in immunogenicity between H-2 haplotypes. We also analyzed human graft rejection times as a function of cross-reactive groups and single specificities (59). The 4c specificity as defined by our serum SA was significantly different but we regarded this more as a statistical than a major biological effect. We also carried out skin grafts in a family in which the patient appeared to be an HLA recombinant. The results were consistent with rejection being most rapid when the HLA-B region was incompatible (60).

In retrospect, these were exciting and often turbulent years marked at times by unselfish cooperation and help and at others by intense competition; I think of this phase as the "pre-Nobel" phase. We laid a solid genetic basis and defined many of the loci and their alleles in HLA, we adopted the concept of the haplotype which appears to be greater than the sum of its parts. For me, the two great unknowns are how to measure the immunogeneity of a haplotype and how to measure the host response to an incompatible haplotype. It may be that interactions with non-MHC loci are extremely important, but this remains for others to decide.

This is a personal recollection and is obviously self-centered because I'm writing about events I participated in and know best. Regrettably, much has been left out and many colleagues, such as Doyle Stulting who was data clerk, programmer, and researcher for an early phase of SEOPF, Max Woodbury and Chinky Johnson who helped with puzzles of cross-reactivity and locus identification, Bill Boyle who was our first immunochemist, Brack Hattler who performed many skin grafts, and Peter Hutchin who traveled hundreds of miles on Piedmont Airlines to read them, are just a few of the many whose participation was invaluable. My especial thanks are due to Donna Kostyu and Fran Ward for reading the manuscript, to Peggy O'Hara who typed it five times, and to Chester Zmijewski, Henry Winn, and other friends who helped straighten out my imperfect memory.

Bernard Amos

Fleming Kissmeyer-Nielsen

Ekkehard Albert

REFERENCES

1. Amos DB, Peacocke N. Leucoagglutination. A modified technique and preliminary results of absorption with tissues. Proc 9th Congr Europ Soc Haemat, Lisbon, 1963. Karger, Basel, 1963; 1132.

2. Phelps HJ. A note on the non-specific action of so-called "anti-cancer" serum. Am J Cancer 1937; 31:441.

3. Lumdsden T. On cytotoxins lethal to nucleated mammalian cells, normal and malignant. Am J Cancer 1937; 31:430.

4. Gorer PA, Lyman S, Snell GD. Studies on the genetic and antigenic basis of tumour transplantation linkage between a histocompatibility gene and 'fused' in mice. Proc R Soc Lond 1948; 135:499.

5. Gorer PA. The antibody response to tumor innoculation in mice with special reference to partial antibodies. Cancer Res 1947; 7:634.

6. Amos DB. The agglutination of mouse leucocytes by iso-immune sera. Brit J Exp Pathol 1953; 3:464.

7. Gorer PA, Amos DB. Passive immunity in mice against C57BL leukosis E.L.4 by means of isoimmune serum. Cancer Res 1956; 16:338.

8. Amos DB, Gorer PA, Mikulska ZB. An analysis of an antigenic system in the mouse (the H-2 system). Proc R Soc Lond 1955; 144:369.

9. Medawar PB. Isoantigens. In: Albert F, Medawar PB, Eds. Biologic problems of grafting. Blackwell, Oxford, 1959; 6.

10. Amos DB, Gorer PA, Mikulska BM, et al. An antibody response to skin homografts in mice. Brit J Exp Pathol 1954; 35:203.

11. Amos DB, Day ED. Passive immunity against four mouse leukoses by means of isoimmune sera. Ann NY Acad Sci 1957; 64:851.

12. Hauschka TS, Amos DB. Cytogenetic aspects of compatibility. Ann NY Acad Sci 1957; 69:561.

13. Amos DB. Some isoantigenic systems of the mouse. In: Proc 3rd Canadian Cancer Conf, Academic Press Inc, NY, 1959; 241.

14. Amos DB, Zumpft M, Armstrong P. H-5.A and H-6.A, two mouse isoantigens on red cells and tissues detected serologically. Transplantation 1963; 1:270.

15. Brent L. Tissue transplantation immunity. Prog Allergy 1958; 5:27.

16. Algire GH, Weaver JM, Prehn RT. Growth of cells *in vivo* in diffusion chambers. I. Survival of homografts in immunized mice. J Natl Cancer Inst 1954; 15:493.

17. Prehn RT, Weaver JM, Algire GH. The diffusion chamber technique applied to a study of the nature of homograft resistance. J Natl Cancer Inst 1954; 15:509.

18. Algire GH, Weaver JM, Prehn RT. Studies on tissue homotransplantation in mice, using diffusion-chamber methods. Ann NY Acad Sci 1957; 64:1009.

19. Amos DB, Wakefield JD. Growth of mouse ascites tumor cells in diffusion chambers. I. Studies of growth rate of cells and of the rate of entry of antibody. J Natl Cancer Inst 1958; 21:657.

20. Amos DB, Wakefield JD. Growth of mouse ascites tumor cells in diffusion chambers. II. Lysis and growth inhibition by diffusible isoantibody. J Natl Cancer Inst 1959; 22:1077.

21. Amos DB. Host response to ascities tumors. In: Mechanism of Cell and Tissue Damage Produced by Immune Reactions. Proc 2nd Int Symp Immunopathol. Benno Schwabe and Co, Basel, Switzerland, 1962; 210.

22. van Rood JJ, van Leeuwen A. Leucocyte grouping: A method and its application. J Clin Invest 1963; 42:1382.

23. Walford RL, Gallagher R, Sjaarda JR. Serologic typing of human lymphocytes with immune serum obtained after homografting. Science 1964; 144:868.

24. Terasaki PI, Mandell M, VandeWater J, et al. Human blood lymphocyte cytotoxicity reactions with allogenic antisera. Ann NY Acad Sci 1964; 120:322.

25. Amos DB, Bashir H, Boyle W, et al. A simple micro cytotoxicity test. Transplantation 1969; 7:220.

26. Brent L, Medawar PB. Tissue transplantation; a new approach to the "typing" problem. Brit Med J 1963; 5352:269.

27. Gray JG, Russell PS. Donor selection in human organ transplantation. Lancet 1963; 2:863.

28. Rapaport FT, Thomas L, Lawrence HS, et al. Skin homograft sensitivity cross-reactions in man. Ann NY Acad Sci 1962; 99:564.

29. Amos DB, Nicks PJ, Peacocke N, et al. An evaluation of the Normal Lymphocyte Transfer Test in Man. J Clin Invest 1965; 44:219.

30. Amos DB, Corley RB, Kostyu DD. The production of antibody against HL-A antigen. Symp Series Immunobiol Standardization 1973; 18:1.

31. Amos DB. Human histocompatibility locus HL-A. Science 1968; 159:659.

32. Tardif GM. SEOPF: The road to a national transplantation program. In: MacQueen JM, Ed. SEOPF Tissue Typing Reference Manual, SEOPF, Richmond, VA, 1987; 1:1.

33. Ward FE, Amos DB, Bias WB, et al. Report on three histocompatibility testing workshops in the Southeastern Regional Organ Procurement Program. Transplantation 1971; 12:392.

34. Amos DB. HLA: A mouser's recollections. In: Terasaki PI, Ed. Clinical Transplants 1989. UCLA Tissue Typing Laboratory, Los Angeles, 1990; 61.

35. Stickel DL, Amos DB, Robinson RR, et al. Renal transplantation with donor recipient tissue-matching. North Carolina Med J 1965; 26.

36. Walford RL, Gallagher R, Troup GM. Human lymphocyte typing with isologous antisera technical considerations and a preliminary study of the cytotoxic reaction system. Transplantation 1965; 3:387.

37. Bain B, McClean LD, Lowenstein L. In vitro test to detect antigenic difference between individuals. Surg Forum 1964; 15:151.

38. Awasaki Y, Osaki A, Fukao K, et al. Withdrawal of immunosuppressive drugs after renal transplantation. A world survey. Transplant Proc 1982; 14:225.

39. Zmijewski CM, Amos DB. A model of leucocyte typing and donor selection for human renal transplantation. Vox Sang 1966; 11:377.

40. Amos DB, Zmijewski CM. Leucocyte typing in kidney homotransplantation. Proc 3rd Cong Nephrol Washington 1966, vol 3, Karger, Basel, 1967; 341.

41. Dausset J, Ivanyi P, Ivanyi D. Tissue alloantigens in humans: Identification of a complex system (Hu-1). In: Histocompatibility Testing 1965, Balner H, Cleton FJ, Eernisse JG, Eds. Munksgaard, Copenhagen, 1965; 51.

42. Amos DB, Hattler BG, Hutchin P, et al. Skin donor selection by leucocyte typing. Lancet 1966; 1:300.

43. Stickel DL, Amos DB, Zmijewski CM, et al. Human renal transplantation with donor selection by leucocyte typing. Transplantation 1967; 5:1024.

44. Zmijewski CM, Amos DB. A comparison of the agglutination and cytotoxicity techniques used for the detection of human leukocyte

isoantigens. Ann NY Acad Sci 1966; 129:558.

45. Amos DB. The inheritance of leucocyte antigens. Transplantation 1967; 5:1015.

46. Amos DB, Cohen I. The inheritance of human leucocyte antigens. II. The recognition of individual specificities of the main system. In: Curtoni ES, Maltiuz PL, Tosi RM, Eds. Histocompatibility Testing 1967, Munksgaard, Copenhagen, 1967; 129.

47. Bach F, Amos DB. Hu-1: Major histocompatibility locus in man. Science 1967; 156:1506.

48. Bach FH, Albertini RJ, Amos DB, et al. Mixed leukocyte culture studies in families with known HL-A genotype. Transplant Proc 1969; 1:339.

49. Plate JM, Ward FE, Amos DB. The mixed leukocyte culture response between HL-A identical siblings. In: Terasaki PI, Ed. Histocompatibility Testing 1970. Munksgaard, Copenhagen, 1970; 531.

50. Yunis EJ, Plate JM, Ward FE, et al. Anomalous MLR responsiveness among siblings. Transplant Proc 1971; 3:118.

51. Yunis EJ, Amos DB. Three closely linked genetic systems relevant to transplantation. Proc Natl Acad Sci USA 1971; 68:3031.

52. Ceppellini R, Curtoni ES, Leigheb G. An experimental approach to genetic analysis of histocompatibility in man. In: Balner H, Cleton FJ, Eernisse JG, Eds. HistocompatibilityTesting 1965, Munksgaard, Copenhagen, 1965; 13.

53. Seigler HF, Stickel DL, Ward FE, et al. Correlations of test skin grafts and renal allograft function in human subjects genotyped for HL-A. Surgery 1970; 68:86.

54. Stickel DL, Seigler HF, Amos, DB, et al. Immunogenetics of consanguineous allografts in man II correlation of renal allografting with HL-A genotyping. Ann Surg 1970; 172:160.

55. Seigler HF, Amos DB, Ward FE, et al. Immunogenetics of consanquineous allografts in man. I. Histocompatibility testing and skin allografts. Ann of Surg 1970; 172:151.

56. Seigler HF, Ward FE, Amos DB, et al. Comparisons of mixed leukocyte reactions with skin graft survival in families serotyped for HLA. Transplant Proc 1971; 3:115.

57. Amos DB, Seigler HF, Southworth JG, et al. Skin graft rejection between subjects genotyped for HL-A. Transplant Proc 1969; 1:342.

58. Amos DB, Andrus CH, Ward FE. A model for determining haplotype immunogenicity. Transplantation 1970; 9:143.

59. Ward FE, Seigler HF, Southworth JG, et al. Immunogenicity of HL-A antigens. In: Terasaki PI, Ed. Histocompatibility Testing 1970. Munksgaard, Copenhagen, 1970; 399.

60. Amos DB, Ward FE, Zmijewski CM, et al. Graft donor selection based upon single locus (haplotype) analysis within families. Transplantation 1968; 6:524.

ABBREVIATED CURRICULUM VITAE

Dennis Bernard Amos

PERSONAL

Born:	April 16, 1923, Bromley, Kent, England

EDUCATION

1951	Guys Hospital, London University, London, England, M.B., B.S. (Medicine), M.R.C.S., L.R.C.P.
1963	Guys Hospital, London University, London, England, M.D. (Pathology)

POSITIONS

1951-52	Intern, Guys Hospital, London
1952-55	Research Fellow, Department of Pathology, Guys Hospital
1955-62	Cancer Research Scientist, Principal Cancer Research Scientist, Roswell Park Memorial Institute, Buffalo, NY
1961-62	Associate Research Professor, University of Buffalo
1962-	Professor of Immunology and Professor of Experimental Surgery Duke University Medical Center, Durham, NC
1963-88	Chief, Division of Immunology, Department Microbiology and Immunology Duke University Medical Center, Durham, NC
1968-	James B. Duke Professor of Immunology and Experimental Surgery, Duke University Medical Center, Durham, NC

AWARDS

3M Life Sciences Award

Albion A. Bernstein Award

National Academy of Sciences

NIH Research Career Award

Institute of Medicine

Professor Honoris Causa, Universidad Federal Do Parana

Rose Payne, Distinguished Scientist Award

PUBLICATIONS

Total: 305

THE EUROTRANSPLANT STORY

J.J. van Rood, A. van Leeuwen, and J.G. Eernisse

Address: Dept. of Immunohaematology & Blood Bank
Bldg. 1, E3-Q, University Hospital
Rijnsburgerweg 10
2333 AA Leiden
The Netherlands

J.J van Rood, A. van Leeuwen, and J.G. Eernisse

J.J. van Rood
in Leiden, 1965

J.J. van Rood **A. van Leeuwen**

THE EUROTRANSPLANT STORY

J.J. van Rood, A. van Leeuwen, and J.G. Eernisse

Eurotransplant is now almost 25 years old and it seems a good time to tell its story. Eurotransplant was the first large-scale effort to implement transplantation immunology and immunogenetics in clinical organ transplantation. Transplantation immunology came into existence thanks to the work of Peter Medawar (1). Figure 1A shows his classical experiments. A piece of skin was exchanged between two rabbits. The skin transplant was rejected after 10 days. When a second piece of skin from the same donor was transplanted to the same recipient, that piece of skin was rejected in five days, and Medawar concluded that the first skin had immunized the rabbit and that homograft sensitivity had been induced. At the time this was still a really new finding which was much debated. The most important experiment however is shown in Figure 1B, which again shows two rabbits, but now no skin from the same donor was exchanged, but the buffy coat of a blood sample from the donor was injected intradermally in the recipient, and only after that was skin transplanted from the same donor. This first transplant was not rejected after 10 days but after five days; in other words an intradermal injection of leukocytes could induce the same homograft sensitivity as a skin transplant. It follows from this that these leukocytes must carry the same transplantation antigens as skin, and with this the whole field of transplantation had been opened. All that remained to be done was to first recognize these transplantation antigens on leukocytes by serological methods and secondly to show that matching for these antigens improved graft survival.

Leukocyte serology, the attempts to recognize the transplantation antigens on leukocytes, started in the fifties (2,3), but it really got its impetus and became effective when it was realized that leukocyte antibodies are formed during pregnancy (4,5).

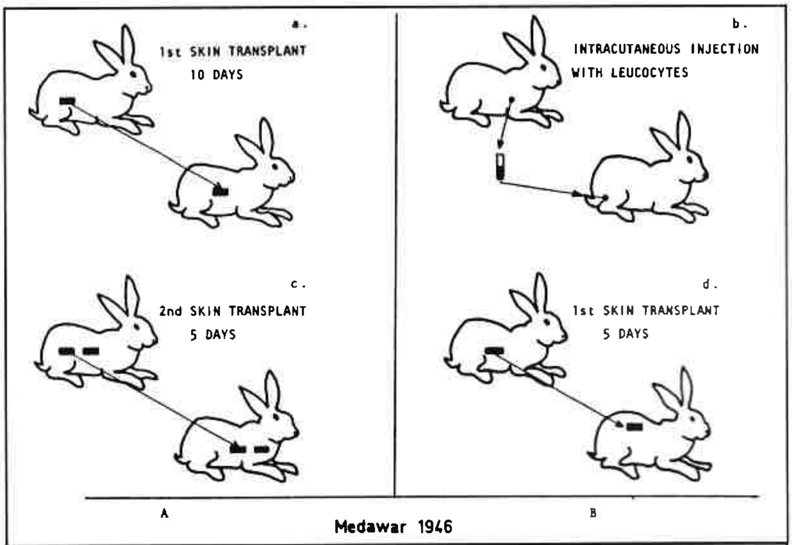


Figure 1. Medawar's classical experiments by which he showed that leukocytes and skin carry the same polymorphic determinants which influence graft survival, ie, transplantation antigens.

With the help of these pregnancy-induced leukocyte antibodies we typed a large panel of 100 donors using 60 sera. Figure 2 shows the results obtained with 34 sera with the leukocytes of the 100 different donors. Unfortunately, the pattern was uninterpretable and it was only after we realized that we needed computer facilities and were able to obtain these, that we could analyze the data. This was done in 1961 and Figure 3 shows what pattern the computer analysis identified (6,7). It has been called the birth of HLA serology. The antigens identified as 4a and 4b have been renamed Bw4 and Bw6, respectively.

Now that we were able to type for polymorphic antigens on leukocytes, the question was: Are they really transplantation antigens? The colleagues who helped us so enthusiastically in unraveling the complexities of the immunogenetics of the transplantation antigens, were now approached and asked whether they would be willing to donate or receive a piece of skin to enable us to answer the question whether these antigens were really transplantation antigens. Fortunately, they all complied. With the help of these colleagues and other volunteers, we were able to repeat Medawar's experiments. The

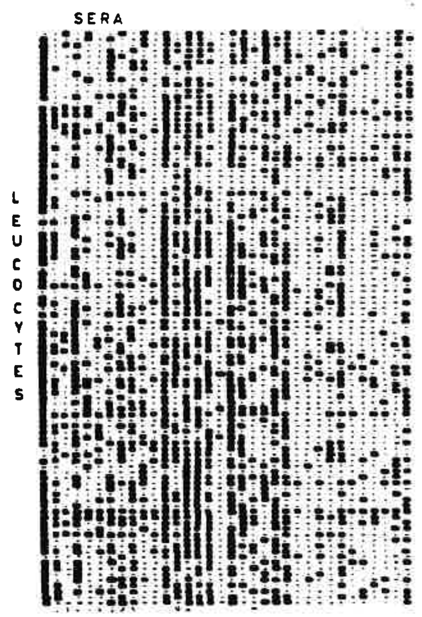


Figure 2. Agglutination pattern of 34 sera with leukocyte antibodies tested against 100 leukocyte samples. Every vertical row of squares and hyphens shows the results obtained with one serum against the panel; every horizontal row shows the results of the 34 sera with one leukocyte sample. Black squares mean agglutination positive; hyphen means agglutination negative. Doubtful results were recorded as agglutination negative (from J.J. van Rood 1963).

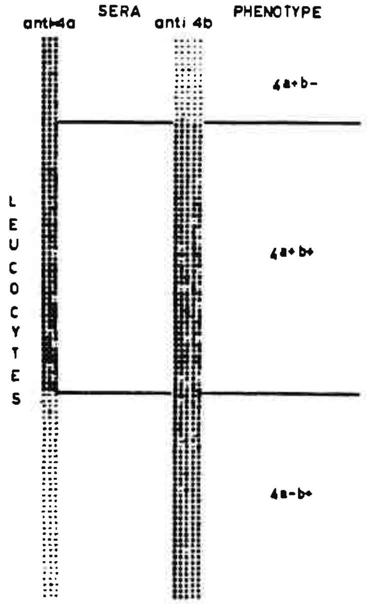


Figure 3. Agglutination pattern of eight sera with the leukocytes of the panel. Every vertical row of squares and hyphens shows the results obtained with one serum against the panel; every horizontal row shows the results of the eight sera with one leukocyte sample. Black squares mean agglutination positive; hyphen means agglutination negative. Doubtful results were recorded as agglutination negative (from J.J. van Rood 1963).

protocol was essentially the same except that we knew whether or not a donor had a certain transplantation antigen. The first HLA antigen which was studied was HLA-B7 then called HL-A7 (8). Table 1 shows that we, like Medawar, injected leukocytes intradermally in the volunteers, waited two weeks, and then transplanted several compatible and incompatible grafts. The compatible graft had a mean survival of 11.6 days, the others six days, and with that we had shown that the antigens we were able to recognize with serology were indeed transplantation antigens. Further studies showed that they also behaved as transplantation antigens in the nonimmunized recipients (9).

In 1966 I discussed our findings with Sir Michael Woodruff, the discoverer of antilymphocyte globulin (ALG). Woodruff became quite enthusiastic and persuaded us to come to Edinburgh to study his patients and so we did. After Edinburgh we set out with Aad van Leeuwen, Ali Schippers, and Hans Bruning on an odyssey around the transplant centers of the world (Fig. 4). We had to be on the spot to be able to do the leukocyte typing because we used an agglutination assay and the cells had to be fresh. In this way we were able to collect data from over 100 patients and their donors.

Table 2 summarizes the analysis of the sibling transplants. Note that we had found far more HLA-identical siblings pairs than expected and far fewer incompatible ones. Not shown is that these 18 patients whom we were able to type came from a group of 40 of which 22 had subsequently died. At that time, if chronic dialysis was not readily available, and if you rejected your kidney, this meant certain death. The conclusion is clear: when donor and recipient are HLA identical it is less likely that the patient will reject the kidney and for that reason he/she remains alive. We had proven with this study (and in a similar study in which the donor was the parent) that the antigens we were able to recognize by serology on leukocytes were not only transplantation antigens important for skin graft survival but also for kidney graft survival. We were very excited. Shortly after the completion of this study the Third Histocompatibility Workshop in Turbin was convened in 1967 by Ceppellini (10). It was at that meeting that the proposal was put forward to set up an international organization for organ exchange: Eurotransplant (11). The name Eurotransplant had come to me when I was passing a big truck on which was written EUROTRANSPORT. Changing only three letters the name Eurotransplant came into existence.

In the beginning the proposal to start Eurotransplant received a rather mixed reception. I must say that with one or two exceptions, my colleagues closest to me were rather skeptical. Perhaps because they knew me best! Anyhow, the idea received the support of quite a few transplant centers, especially in Belgium. The first kidney was transplanted in September 1967, much earlier really than we had planned. It was flown in by helicopter from Louvain. In 1967 a total of 11 kidneys was transplanted under the auspices of Eurotransplant. In 1968 this number rose to 60 and then steadily increased. This period was really fun. There was a close cooperation between surgeons, nephrologists, and immunologists. Each patient was discussed before selection for transplantation, and the whole team was activated when a kidney became available. I remember quite well the direct involvement with the transplant procedure and how I enjoyed it.

The first analyses of the Eurotransplant data were presented at the meeting of the International Transplantation Society in The Hague in 1970. The meeting became quite famous, not so much for its scientific importance as well as for the very liberal availability of Dutch beer and gin and the excellent social program. I was supposed to give an overview of the activities of

Table 1. Recipients were HL-A7 negative and immunized with HL-A7 positive leucocytes.

Immunized dose (leuc.)	Interval (days)	Survival of Skin Graft	
		HL-A7 pos.	HL-A7 neg.
1.2x10^8	14	0	12
2.2x10^8	18	5	9
2x10^8	16	5.5	8.5
0.5x10^8	13	7	14
2x10^8	14	9	11
2.1x10^8	14	9.5	11.5
Mean		6	11

[*Histocompatibility Testing 1965.* Copenhagen, Munksgaard, 1965; 37.]

Eurotransplant at that meeting. However, when we analyzed our data we found that there was really very little to be said about the effect of matching. One thing we noted though was that our results were much better than those reported by the International Registry for Kidney Transplantation (Fig. 5) (12). At the time we assumed that this was due to our better-than-average matching, but we had no hard data to support this.

With a longer follow-up, however, it became clear that in these first years we had also improved long-term graft survival (Fig. 6). An analysis by van Hoof showed a clear indication of the excellent transplant survival of the patients who were well matched with the donor when compared to those who were only compatible or fully mismatched (13). Also a check on the relation between lymphocyte infiltration and matching showed that the better they matched the fewer lymphocytes infiltrated the kidney.

This might be a good moment to point out that we typed at the time for the so-called Leiden antigens, the first series to be described. Table 3 shows the modern equivalents of these antigens. Note that the old Leiden antigens were what we now call cross-reacting antigens. We were in fact mainly matching for the cross-reactive groups of the HLA-B locus together with A2 and A28. Recently Sanfilippo has shown that matching for these cross-reacting antigens is indeed of interest, especially because the results are almost as good as

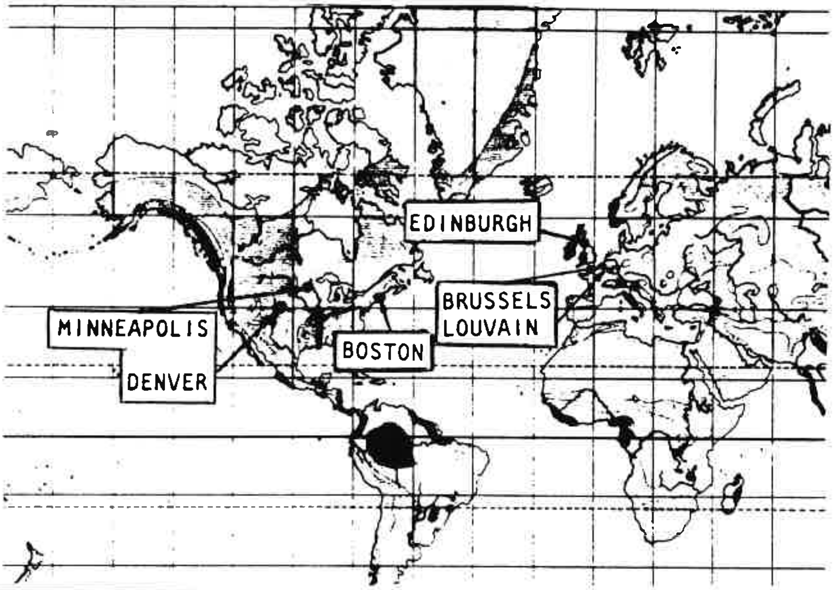


Figure 4. Centers which collaborated in the first retrospective HLA typing study of family transplants.

Table 2. HLA matching in survivors of living-related transplants.

	Patients	
	Found	Expected
Identical	9	3.6
Compatible	3	3.4
Incompatible	6	11.0
Sib-to-Sib		

[*Histocompatibility Testing 1967*. Baltimore, Williams & Wilkins, 1967; 203.

Table 3. The "Leiden antigens" (Group Four system)

4a=Bw4+A9	4b=Bw6
6a=7b (-B12)	6b=B7+B13+B22+B27+B40
7a=B15	7b=B5+B12+B15+B18+B21+B35
	7c=B7+B27
	7d=B8
8a=A2+A28	

[Histocompatibility Testing 1967, Baltimore, Williams & Wilkins, 1967; 203.

matching for the private antigens (14). Of course, it is much easier to obtain good matches if one has to match only for cross-reactive antigens.

And this is the Eurotransplant story as I record it here: really not much more than an introduction and a first chapter. Many chapters followed and will be recorded elsewhere: the chapter on pretransplant blood transfusion, the (hyper) immunized patient, Ir gene effects in organ transplantation, minor antigens, tolerance, and much more. Working with Eurotransplant remained, as in the early days, an exciting and rewarding adventure.

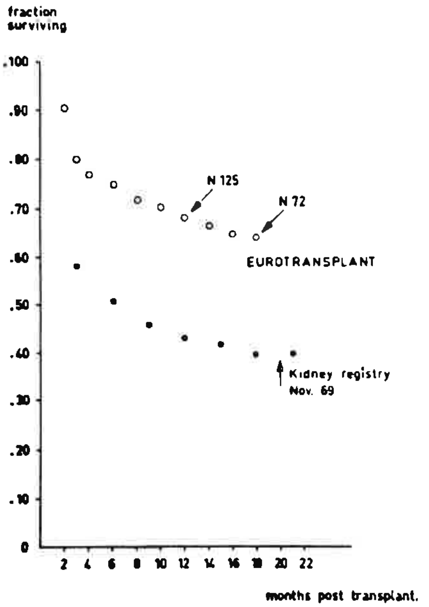


Figure 5. Kidney graft survival in Eurotransplant (0). Of the 125 grafts performed 68 percent functioned after one year. The graft survival published in the 1969 Kidney registry report is given as well.

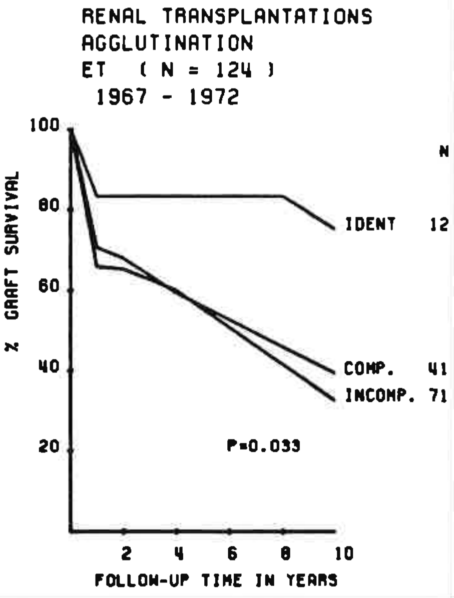


Figure 6. Long-term follow-up of the first 134 kidneys transplanted under the auspices of Eurotransplant. Transplants from donors which were identical with the recipient for the nine cross-reactive antigens then recognized did significantly better than those which were compatible or incompatible.

REFERENCES

1. Medawar PB. Immunity to homologous grafted skin. II. The relation between the antigens of blood and skin. Br J Exp Pathol 1946; 27:15.

2. Miescher P, Fauconnet M. Mise en evidence de differents groupes leucocytaires ches l'homme. Schwiez Med Wschr 1954; 84:597.

3. Dausset J. Leuko-agglutinins. IV. Leuko-agglutinins and blood transfusion. Vox Sang 1954; 4:190.

4. van Rood JJ, Eernisse JG, van Leeuwen A. Leukocyte antibodies in sera from pregnant women. Nature 1958; 181:1739.

5. Payne R, Rolfs MR. Fetomaternal leukocyte incompatibility. J Clin Invest 1958; 37:1756.

6. van Rood JJ, van Leeuwen A, Bosch LJ. Leukocyte antigens and transplantation immunity. Proc Eighth Congress Eur Soc Haematology, Vienna 1961, 1962; 199.

7. van Rood JJ, van Leeuwen A. Leukocyte grouping. A method and its application. J Clin Invest 1963; 42(9):1382.

8. van Rood JJ, van Leeuwen A, Schippers AMJ, et al. Leukocyte groups, the normal lymphocyte transfer test and homograft sensitivity. In: Histocompatibility Testing 1965. Copenhagen, Munksgaard 1965; 37.

9. van Rood JJ, van Leeuwen A, Schippers A, et al. Leukocyte groups and their relation to homotransplantation. Ann NY Acad Sci 1966; 129:467.

10. van Rood JJ, van Leeuwen A, Schippers AMJ, et al. Immunogenetics of the group four, five and nine system. In: Histocompatibility Testing 1967. Baltimore, Williams and Wilkins 1967; 203.

11. van Rood JJ. A proposal for international cooperation in organ transplantation: Eurotransplant. In: Histocompatibility Testing 1967. Baltimore, Williams and Wilkins 1967; 451.

12. van Rood JJ, van Leeuwen A, Freudenberg J, Rubinstein P. Prospects in host-donor matching. Transplant Proc 1971; 3:1042.

13. van Hoof JP, van Leeuwen A, Paul L, et al. The influence of matching for broadly reacting antigens on long-term kidney graft survival. Transplant Proc 1985; 17:2205.

14. Sanfilippo F, Vaughn WK, Spees EK, et al. Benefits of HLA-A and -B matching on graft and patient outcome after cadaveric-donor renal transplantation. N Engl J Med 1984; 79:358.

CURRICULUM VITAE

Johannes Joseph van Rood

PERSONAL

Date of birth:	April 7, 1926
Nationality:	Dutch
Place of birth:	The Hague, The Netherlands
Married:	Sacha Baronesse van Tuyll van Serooskerken
Children:	Yanda, Peter and Tinka
Home address:	Laan van Alkemade 3, Oegstgeest, The Netherlands
Office address:	Department of Immunohaematology & Blood Bank, Bldg. 1, E3-Q, University Hospital, Rijnsburgerweg 10, 2333 AA Leiden, The Netherlands
Tel. No.:	(0)71-263800/263827

MEDICAL TRAINING

1945-52	University of Leiden (medicine)
1950	Department of Medicine (Dr. R.F. Loeb), Presbyterian Hospital, Columbia University, New York, N.Y., U.S.A.

RESIDENT AND POSTGRADUATE TRAINING

1952-57	Department of Medicine, University Hospital, Leiden
1953	Training in blood banking, Central Laboratory of the Dutch Red Cross Blood Transfusion Service, Amsterdam
1957	Specialist in Internal Medicine (equivalent to US Board Examination). In charge of Blood Bank and Department of Immunohaematology, University Hospital, Leiden
1958-	Engaged in tissue typing
1962	Doctor of Medicine (cum laude) (equivalent to US Ph.D. or Doctor of Medical Science); thesis: "Leucocyte Grouping. A method and its application" (Prom.: Prof. Dr. J. Mulder).
1962-63	Sabbatical year in the Department of Immunology, Public Health Research Institute of the City of New York., N.Y., U.S.A. (head: Dr. F.L. Adler)
1981	Certificate "Immunology" of the Registry of Immunologists of the Dutch Society of Immunology
1986 (Feb-Apr)	Sabbatical, Department de Microbiologies C.M.U. Faculté de Médecine Genève

APPOINTMENTS

1957-	Head of the Department of Immunohaematology
1965	Lecturer in Internal Medicine
1967	Founder and President of the Eurotransplant Foundation
1969	Professor of Internal Medicine

1976	Chairman of the Department of Haematology
1985	Founder and President of the European Foundation of Immunogenetics
1986-	Guest Professor "Vrije Universiteit" Bruxelles
1986	Co-founder and Chairman of Leiden Institute for Immunology
1987	Supervisor for the training of Immunology postgraduate students

ADVISORY COMMITTEE MEMBERSHIP, EDITORIAL BOARD, ETC.

Advisor of the Primate Center TNO, Rijswijk, The Netherlands

Member of the "Working party on the exchange of sera for the determination of histocompatibility" of the Council of Europe

Member of the Royal Dutch Academy of Sciences (section Physics, since 1978)

Member of the International Scientific Council of the "Foundation Cardiologique Princesse Liliane"

Member of the Advisory Board of Tissue Antigens

Member of the Advisory Board of Transplantation Proceedings

Member of the Editorial Board J. Immunopharmacology & Immunotoxicology

Member of the Editorial Board of Immunology Letters

Member of the Editorial Board of Thymus

Member of the Editorial Advisory Board of Current Titles and Abstracts in Immunology, Transplantation and Allergy (CTAITA)

Associate Editor Bone Marrow Transplantation

European Editor of Human Immunology (from 1/9/1982)

ESHI Member Advisory Board European School of Hematology

Member of the "Stiftungsrat der Paul Ehrlich-Stiftung"

Member of "Scientific Advisory Committee of the Anthony Nolan Laboratories"

Member International Advisory Committee Netherlands Cancer Institute

Member of the Academia Europaea

AWARDS

1973	Recipient of the Dutch Kidney Foundation Prize
1977	Recipient of the Karl Landsteiner Memorial Award
1977	Recipient of the German "Spende eine Niere" Prize
1977	Recipient of the Robert Koch Medaille
1978	Recipient of the Wolf Prize
1980	Price of the Dutch Federation of Medical Research Societies
1985	Recipient of the Artois-Baillet Latour Price for the Benefit of Health, Brussels
1989	Recipient of the E. Jung-Prize for Medicine, Hamburg
1990	Recipient of the James Blundell Award of the British Blood Transfusion Society, London
1990	Recipient of the Amsterdam Prize for Medicine of the Royal Dutch Academy of Sciences

HONORARY LECTURES

1967	John G. Gibson II Lecture for Columbia University
1983	Heberden Oration for the Heberden Society, London
1984	Recipient of the Franz-Oehlecker-Medaille of the Deutsche Gesellschaft für Bluttransfusion and Immunhamatologie e.v.
1990	Niels Jerne Lecture, Les Embiez
1990	P. Grabar Lecture, Paris

HONOURS

1968	Doctorate Honoris Causa of the Faculty of Medicine of the University of Santiago de Chile, Chile
1970	Distinguished Service Decoration of the Dutch Red Cross
1972	Korrespondierend Mitglied Deutsche Gesellschaft für Bluttransfusion
1979	Honorary Member of the American Association of Immunologists
1980	Honorary Member of the Scandinavian Society of Immunology
1980	Doctorate Honoris Causa of the Faculty of Medicine of the University of L'Aquila, Rome
1980	Doctorate Honoris Causa of the Faculty of Medicine & Surgery of the University of Torino
1981	Doctorate Honoris Causa of the University of Maastricht, the Netherlands
1982	Doctorate Honoris Causa of the Faculty of Medicine of l'Université Claude Bernard de Lyon, France
1984	Corresponding Member of the Royal Academy for Medicine of Belgium, Brussel
1984	Doctorate Honoris Causa of the Faculty of Medicine of the "Katholieke Universiteit" of Louvain
1985	Doctorate Honoris Causa of the Faculty of Medicine of the Medicine of the "Université Catholique de Louvain", Louvain
1985	Recipient of the Order of Knighthood of the Dutch Lion
1988	Doctorate Honoris Causa of the Faculty of Medicine of the University of Essen
1989	Fellow of the Royal College of Physicians, London

RESEARCH ACTIVITIES have centered around the following topics:

1. Genetics of histocompatibility antigens
2. Organ and bone marrow transplantation
3. Genetic factors in disease
4. Bloodbanking
5. Clinical haematology
6. Clinical immunology

SYNOPSIS OF RESEARCH ACTIVITIES

In the last decade, a multitude of studies has shown that the HLA system plays an important role in the efficacy of blood component therapy, the prognosis of organ grafts and in the susceptibility for or the resistance against a great number of infectious and non-infectious diseases.

These studies were all dependent on the possibility to recognize the HLA system. The recognition of the HLA system only became possible in the early sixties. Before that time several workers (Miescher, Dausset, Payne, Van Loghem, Lalezari, Van Rood) had shown that antibodies against leucocyte alloantigens could be induced by blood transfusion and/or pregnancy. Although Dausset (the antigen Mac), Miescher and Lalezari presented formal proof that the antibodies were alloimmune antibodies and recognized white cell antigens, the leucocyte antibodies proved difficult to work with and a systematic approach to classify leucocyte antigens was lacking. This changed in 1962 when Van Rood published such an approach.

In brief, the sera from a large number of women who had formed leucocyte alloantibodies during pregnancy were tested against the leucocytes obtained from 100 unrelated donors. A computer-assisted search identified two clusters of sera with high internal consistency i.e. they reacted or did not react with the leucocytes of approximately the same donors. The determinants so recognized were of contrasting specificity and could be shown to be coded for by allelomorphic genes. They are now known as HLA-Bw4 and -Bw6.

The importance of this discovery did not lie only in the fact that it was a first description of diallelic antigens in the HLA system but also and above all in providing a systematic approach by which the complexity of the HLA system could be unravelled. Using this approach, Van Rood and collaborators described a total of 9 HLA antigens and a diallelic system not linked to HLA (the group Five system). Using the same approach, Payne and Bodmer detected three additional antigens. Together with Balner, Van Rood demonstrated that these leucocyte antigens were in fact transplantation antigens. In 1965, Dausset et al. again using the same approach, described several additional antigens. At the same time but independently, Dausset and Van Rood suggested that the majority of these antigens might belong to one system; Dausset on the basis of association data, Van Rood on family data.

An intensive international cooperation made it possible to unravel the complexity of the HLA system further.

During these studies it became evident through observations by Amos, Bain, Eijsvoogel, Yunis and notably Bach, that the HLA system coded for determinants which were able to induce blast formation in allogeneic T lymphocytes. These determinants are coded for by the HLA-D locus and can be studied in the MLC test originally described by Bach, et al and Bain, et al.

In 1973 Van Rood and his collaborators described a serological method to identify antibodies which reacted with these HLA-D determinants or closely related structures. They are referred to as the HLA-DR determinants. Many of the genes which predispose for the diseases mentioned above, are identical to or closely associated with these HLA-DR genes.

During the studies on the genetic complexity of the HLA system, a conscientious effort was made to implement the information so obtained in clinical and preventive medicine, as can be exemplified as follows:

1. The first HLA matched platelet transfusions in the treatment of aplastic anaemia were given in Leiden in 1964.
2. After demonstrating in a retrospective study that HLA matching could improve kidney graft survival, the Eurotransplant organization was established in 1967 by Van Rood. Eurotransplant is an international organ-exchange organization which operated as

follows: the leucocyte groups and other pertinent clinical and administrative information from patients awaiting a renal transplantation are stored in a central computer databank. Whenever a postmortal donor becomes available anywhere within the Eurotransplant area, a matching program indicates the location of the most suitable (HLA compatible) recipients. Following example of Eurotransplant, national (Francetransplant and UK-transplant) and supernational organ-exchange organizations (Scandiatransplant) have been established. Eurotransplant maintains close contact with those organizations.

The results obtained in the Eurotransplant area are among the best in the world and enable many patients who otherwise would have to be treated by an artificial kidney to lead an (almost) normal life. The activities in Eurotransplant have not only led to improved patient care but also provided new possibilities for (clinical) research.

These included a possible explanation for the pretransplant blood transfusion effect. This seems to be dependent on a sharing of a class II or HLA-DR antigen between bloodtransfusion donor and recipient. A follow-up of this study has shown that non-inherited maternal antigens might induce a form of (partial) tolerance of the child towards the mother. This has possibly important consequences for organ and bone marrow transplantation and the pathogenesis of autoimmune diseases.

3. The Leiden group has from the beginning played an active role in supporting the establishment of numerous tissue typing centers within and outside Europe. Some of the more important centers are found in London (St. Mary's Hospital), Belgium (3x), Germany (7x), Turin, Oslo, Zurich, South-Africa (3x), North America (3x), Montreal, South America (2x), Australia (3x), Singapore, New Delhi, Tokyo, Moskow, and Budapest.

4. The application of the HLA matching in bone marrow transplantation also started in Leiden. The first bone marrow transplants which were performed there were done at the time that importance of HLA matching in organ transplantation was not yet clear. However, soon afterwards findings in Leiden itself and those from other countries established without doubt that matching for HLA made all the difference.

Perhaps the most clear cut data came from the studies in children suffering from immunodeficiency. Without exaggeration it can be stated that HLA matching revolutionized the treatment of children with immunodeficiency by bone marrow transplantation. The first successful cases were performed in Minneapolis (Good, Bach) and in Leiden (De Koning, Dooren, Van Rood and others). Thanks to these activities, survival of SCID patients who have an appropriate donor is well over 80%.

However, many of the children suffering from immunodeficiency do not have an appropriate donor. Van Rood suggested already in 1974 (Transplant Proc. VI 4: 411, 1974) to come to organizations similar to that of Eurotransplant but now called Europdonor. The genetics, mathematics, and logistics of such an organization we worked out in detail.

At the moment in Europe there are only about two hundred thousand donors who are suitable to be used for bone marrow transplantation, have been HLA typed and have given permission to be contacted if a patient in need of bone marrow cells of their HLA type is presented. A part of the effort of this organization is embedded in the European Bone Marrow Transplant Group, an initiative of Van Rood, Speck and others, in which teams working in bone marrow transplantation and leucemia, aplastic anemia, autologous marrow transplantation and transplantation immunology and immunodeficiency collaborate through multicenter protocols and meetings.

Van Rood has been the Chairman of the latter group since the start of the European Bone Marrow Transplant Group. One of the goals of the organization is to actively support and stimulate the use of unrelated donors in bone marrow transplantation for patients suffering from immunodeficiency. To this end Van Rood persuaded the 10 different bone marrow donor organizations to pool the information on these donors in one single publication: "Bone Marrow Donors Worldwide", which has been widely distributed in Europe and the USA.

5. HLA and disease.

   The Leiden group has from the beginning been involved in the study of the relationship of HLA and disease, such as leucemia, Morbus Hodgkin, gluten enteropathy, ankylosing spondylitis and others. A concerted effort has been made in the last years to study the genetic factors involved in the occurrence of major endemic diseases. A model for such studies was leprosy. About 12 million people are suffering from this disease in which failure of cellular immunity plays a major role. Systematic studies from the Leiden group have brought forward the following important points:

   a. The genetic predisposition for the disease is probably not governed by the HLA system but by a locus or loci outside the HLA system.
   b. The HLA system does play a role, however, in determining in patients who have been infected whether they get the lepromatous or the tuberculoid form of the disease. The tuberculoid form of the disease is far more frequent in patients who are carrying the DR3 antigen.

HISTOCOMPATIBILITY

Paul I. Terasaki

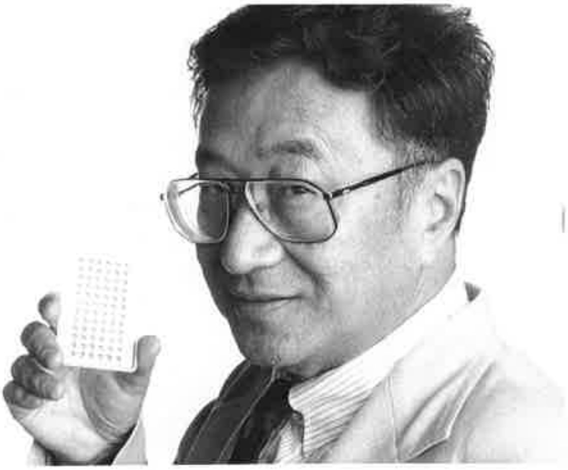
Address: UCLA Tissue Typing Laboratory
950 Veteran Avenue
Los Angeles, California 90024

Paul I. Terasaki

ca. 1980

Paul Terasaki Thomas Starzl Sir Roy Calne

Japan Transplant Society, 1985



1990

HISTOCOMPATIBILITY

Paul I. Terasaki

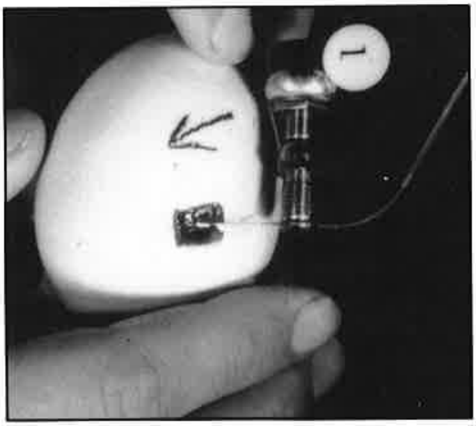
I consider myself supremely fortunate that my M.A. and Ph.D thesis on the transplantation of a rabbit tumor was the start of my work in the field of transplantation - an endeavor that was to keep me at UCLA for a total of 43 years.

Prof. Abraham Schectman

Abe Schechtman was a unique embryologist whose main interest was using newly developed immunologic tools to reinvestigate elusive problems of ontogeny. It was his encouragement that propelled me into work on transplantation. Thanks to his generosity, I narrowly passed my Ph.D. exams. Tragically, he succumbed to a brain tumor early in his career.

Prof. William Longmire

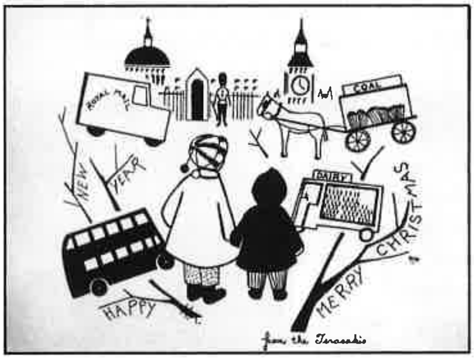
Dr. William Longmire, one of the founders of the UCLA Medical School in 1950, was Chairman of the Department of Surgery for the first 35 years of the newly formed school's growth. Transplantation was one of his pet projects, carried forward from his skin graft studies at Johns Hopkins. There he had shown that the diversity of tissue types must be very large, for none of the skin transplants from many random persons onto a burned patient had survived (1). In 1952, he and Jack Cannon demonstrated that allografts interchanged between newborn chicks can survive permanently (2), before the now classical studies of Billingham, Brent, and Medawar on neonatal tolerance (3).



Starting work in the Department of Surgery in 1955, I spent about two years cross-transfusing chick embryos and performing tolerance (3) and graft-versus-host experiments (4). In my youthful immersion in the work, I labored under the delusion that I was doing original work and didn't realize for some time that I was merely confirming the work of Billingham, Brent, and Medawar. Somehow I had to get out of this predicament. I asked Dr. Longmire for permission to go to work with the London group. He was enthusiastic and immediately wrote to Peter Medawar on my behalf. Sadly the answer came back that there was no room for me.

If I couldn't go to London, I thought I should at least discuss our experiments with Leslie Brent, who was spending a year at Ray Owen's lab at Cal Tech in Pasadena. It was a high for me to meet Ray Owen and Leslie Brent and hear their comments on my experiments. About a month later, I was amazed to hear from Peter Medawar himself, saying that he managed to make space for me for a fellowship. I had not talked to Brent with any hope of getting to London, but apparently he had passed along a positive recommendation to Medawar. Leslie Brent was to return to London and help guide me through the culture shock I experienced being outside of the United States for the first time. Everything, including the language, seemed so different in England.

Prof. Leslie Brent



In this drawing sent from London on our first Christmas away from home, my wife captured the awe of our two small kids. How very fortunate we were that Mrs. Jean Medawar had found us a flat on Hampstead Heath. Memories of this marvelous year were sufficient to last us for the next 30 years in Los Angeles, sans sabbatical.

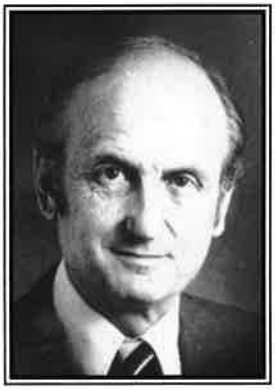
Searching for the reason why this remarkable year was so valuable to me, I tried to pinpoint the essence of the experience. My own assessment of the Medawar genius, gained from that one brief year, is best illustrated by a comment he made when I went to him with an exciting new idea for experiments. He asked, "But if all went well, are the conclusions important?" His question has recurred to me through the 30 subsequent years and it fits with the saying, "It's even more important to do the RIGHT project than to do it right." It seems to me that Peter Medawar consistently managed to work on the most important issues; of course, with the caveat that they were solvable, given the knowledge at that time. For example, he was the first person to work on chemically identifying the histocompatibility antigens, starting about 1958 (5). Although his conclusions were later proven wrong, it was he who led a horde of investigators into the search for ways to solubilize and chemically define the antigen.

It was my good fortune to work with Medawar in the days before his knighthood and Nobel Prize. As mentioned in his chapter, it was in 1969, at the height of his extraordinarily creative life, that a stroke prematurely curtailed his brilliant career.

Peter Medawar

Since that memorable year in London, all of my work in the ensuing 30 years was done at UCLA with the strong support of Drs. William Longmire, Chairman of the Department of Surgery; Sherman Mellinkoff, Dean of the School of Medicine; and Frederick Rasmussen, Associate Dean. Many were the times when I needed more space and support to overcome difficulties, and without encouragement from the top, it is doubtful that I, along with my many long-term associates within the laboratory, could have sustained our efforts.

Dean
Sherman Mellinkoff



Assoc. Dean
A. Frederick Rasmussen

Our main transplant projects during these last 30 years could be divided into the following six segments: 1) microcytotoxicity test, 2) simple cold storage and kidney sharing, 3) HLA definition, 4) crossmatch, 5) histocompatibility, and 6) analysis of transplant factors.

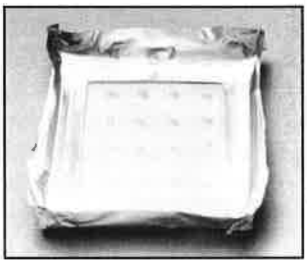
1) THE MICROCYTOTOXICITY TEST

While working in London, somehow I came to the conclusion that humoral immunity was more important than cellular immunity, which was contrary to Medawar's and Brent's view. Rather than work with cells as effectors, I wanted to use them as targets of antibodies and try to tissue type people. To this day, I'm not sure whether this view was simply youthful rebellion against prevailing opinion. My resolve was shown by my asking Dr. Longmire for an extension of my fellowship to go from London to Paris to work with Jean Dausset, who was working on antibodies, though in the context of transfusion reactions rather than transplantation.

By 1958, Dausset had shown that he could detect leukoagglutinating antibodies in the sera of transfused patients. Although I had planned to spend some time with Dausset, I actually wound up at the Pasteur Institute, working with Dr. Jacques Oudin. He was a kindly, inspiring type of scientist, though his interests were different from mine. After three months, feeling as though I was getting nowhere with my objectives, we gave up our apartment in Auteuil (and the wonderful baguettes) and came home to UCLA.

Perhaps it was just as well that I did not work under Dausset because I had already formed an opinion that the leukoagglutination test he was using was flawed. When I returned, I immediately started working on an agglutination test using lymphocytes (6), which avoided the nonspecific reactions produced by granulocytes. This was effective with chickens, but to my disappointment, lymphoagglutinating antibodies could not be produced by alloimmunization of mice or rabbits. We spent four intense years working out the optimal conditions for the lymphocyte cytotoxicity test on rabbits (7) and mice (8). Many hours in the laboratory were required to learn what would NOT work, despite publications to the contrary. I was absolutely convinced that the leukoagglutination method, then used by leaders such as Dausset, Payne, Van Rood, and Ceppellini, was too capricious for use in clinical typing.

The lymphocyte microcytotoxicity test was developed with John McClelland in 1964 (9). The first tests were done in an oil chamber formed by taping an aluminum foil edge onto a coverglass. The dots composed of serum, cells, and complement were examined from below with an inverted phase contrast microscope. In attempts to type actual kidney transplant patients, often the number of lymphocytes was very limited. Typing reagents were also extremely valuable. We settled on using the smallest unit which could be dispensed - 0.001 ml, or one lambda (roughly the volume enclosed by the letter o). Evaporation of such a small amount was the most difficult aspect and use of an oil chamber was the key solution.



The lymphocyte microcytotoxicity test was demonstrated at the First Histocompatibility Workshop at Duke University. Only Ceppellini recognized the value of the test, and he immediately took steps to change over by sending Dr. Hammond to learn this test during his sabbatical so he could import it to Italy. By the time of the Second International Histocompatibility Workshop in Leiden, nine labs used the leukoagglutination method, seven used lymphocyte cytotoxicity, and only Ceppellini and our lab used the microcytotoxicity test. Roy Walford soon adopted the test, and during his sabbatical year in Paris, he introduced it to Dausset.

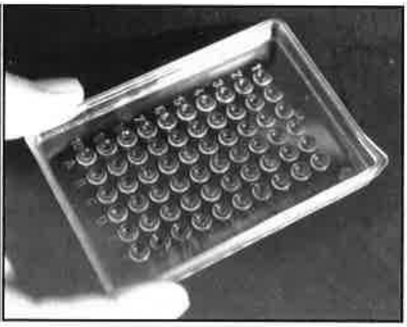
John McClelland

Peter Morris *John McClelland* *Paul Terasaki* *Ruggero Ceppellini*

At the Third Torino Workshop in 1967, Dr. Peter Morris and John McClelland, who were on our team, demonstrated the latest advances in performing the microcytotoxicity test to Ceppellini and the others. It was the test that half of the labs had converted to, and by the Fourth International Workshop (which we sponsored in Los Angeles in 1970), all labs had agreed to use the microcytotoxicity test EXCLUSIVELY.

Most of the conditions that Dr. Kamal Mittal, working in our laboratory, had established by 1968 (10) were adopted as a standard at an NIH meeting (11); hence, the test is often called the NIH test.

Kamal Mittal

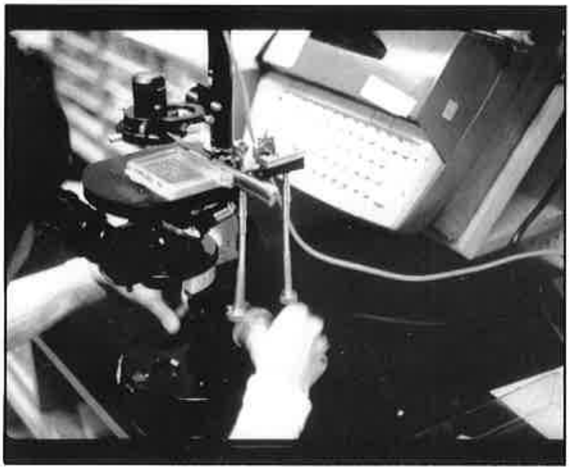


After many modifications, the plastic tray in common use today was produced in 1967. The tray was designed so that every cell in the well could be seen through the microscope at one glance. It also facilitated the development of various automation devices. Although the University felt that a patent on the tray would not be profitable, we estimate that today, over 10 million trays per year are being manufactured.

Since 1970 the microcytotoxicity test has been the standard by which all HLA typing antisera were selected for use in typing by all six subsequent International Histocompatibility Workshops. The ability to perform 1,000 tests from 1 ml of precious antisera permitted the massive exchange of sera during the workshops.

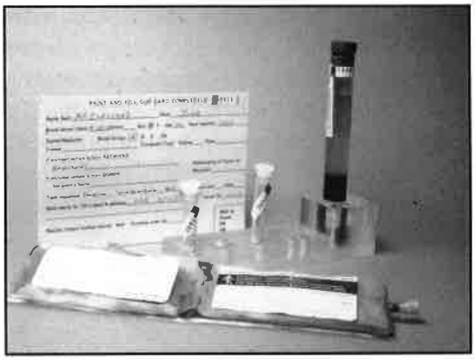
For the past 20 years, ALL kidney and bone marrow transplants have been typed by this test. It is essentially the only test used for the determination of HLA types for various other purposes. There have been some challenges, but the test has survived virtually unchanged for 26 years (11).

A history of the development of the test appears elsewhere (12), but the following is a brief summary.



The most important technical knowledge I gained during my 1958 postdoctoral year with Peter Medawar was the use of the phase contrast microscope. When properly adjusted, phase contrast was a marvelous way to look at living cells. It was easy to see the nonspecific granulocyte agglutination and loss of viability after one day. We devised a button system to run an electric typewriter so that one need not look away from the scope to record the reactions.

I was convinced from the outset that we would not obtain the answers concerning efficacy of tissue typing to match donors and recipients by testing patients from only one center since the number of patients who could be transplanted at one center was limited. We needed a simple way to transport blood from distant centers to Los Angeles. In our earliest system, glass beads in a plastic bag served to soak up blood and hold it, just as wet sand holds water, and the bag was then put into an airmail special delivery envelope. Upon receipt, the beads were poured into a cup with a nylon mesh below. Granulocytes stuck to the glass beads during shipment, and lymphocytes could then be flushed through.



Subsequently, a two-chamber plastic bag was developed wherein the granulocytes stuck to the nylon wool in the first chamber upon short incubation. The remaining lymphocytes and red cells were flushed through to the second chamber which contained a tampon. This later invention was a much lighter and more secure absorbent than glass beads, but it took a giant vise to then squeeze the blood out.

With this system, we undertook the systematic typing of essentially all the kidney transplants that were being performed in the United States from 1965 to 1968. A report of typings on 196 kidney transplant patients and their donors from seven centers was summarized at the Santa Barbara Transplant Meeting in 1967 (13). By 1970, the largest series of 1216 transplant patients from 52 centers was accumulated for analysis (14). It was only the lymphocyte microcytotoxicity test that made it possible to ship the cells and do the tests in a centralized location. Laboratories that did not convert to the lymphocyte microcytotoxicity test were unable to come to any conclusion by this early date.

In summary then, the lymphocyte microcytotoxicity test made it possible to test thousands of alloantibodies against large panels of cells and to type large numbers of patients. The existence of 100 or more HLA antigens has made it essential that a simple microtest be available for such mass testings. Transplants were also being performed in large numbers, and it can be estimated that over one million actual and potential donors and recipients have been typed. It was fortuitous that the revolution in computer technology was occurring during this exact period. For without computers, data analysis of the thousands of reactions which were now possible to generate could not have been harnessed.

2) COLD STORAGE AND KIDNEY SHARING

From the earliest work in tissue typing, it rapidly became apparent that there would be no hope for the application of tissue typing to the performance of matched transplants without a large pool of recipients. With such an enormous number of antigens to be matched, it would be unrealistic to imagine that a particular cadaver donor in any given city would be matched with a local waiting recipient. We reasoned that inasmuch as cooling to slow down the metabolism in the donor organ was a most important factor in kidney preservation, if the right flush media could be found, mechanical perfusion should be unnecessary.

In 1967, with Drs. Donald Martin and Ian Gray, we started experiments to preserve dog kidneys by simple cold storage.

In 1968 we were joined by Dr. Geoffrey Collins, who had just completed his surgical residency in England. At the start of the project there were many failures, but after operations on a total of 200 dogs, we finally arrived at the ideal preservation solution, called C4 (15). Aside from the hard work, I believe our success resulted from deciding in advance that our model would be maintaining the preserved kidney's daily normal serum creatinine values for one week in the bilaterally nephrectomized dogs. The model was unforgiving of any technical errors or inadequacy of the preservation solution.

Dr. Geoffrey Collins

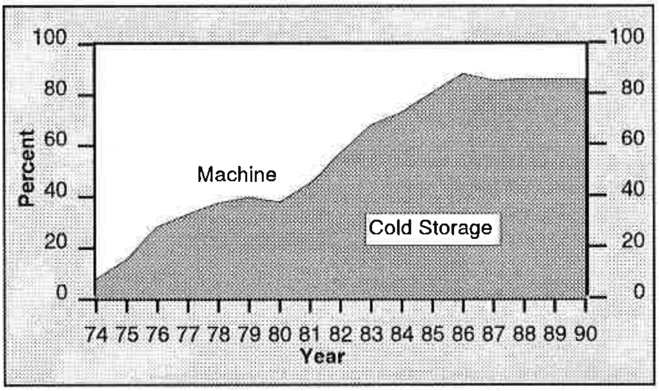
Once the methods were worked out, we sought to convince others of the workability of simple cold storage. At that time, the only storage method was pulsatile perfusion using either the Belzer machine or the Van Waters perfusion machine. Pulsatile perfusion was so well entrenched that very few surgeons were willing to consider a method as primitive as cold storage. The objection in the Los Angeles area was that our little cardboard box with ice would be offensive to the operating room personnel who were accustomed to the Belzer Machine Ambulance with its impressive machine, paraphernalia, and perfusion technologists. To add insult to injury, we suggested that the kidney be sent from the harvesting hospital by ordinary messenger service.

In our desperation to have the cold storage method accepted, dog kidneys were sent by ordinary air freight to Dr. Collins who went around the world implanting kidneys in London, Tel Aviv, and Sydney (16). As shown, the Los Angeles kidneys functioned immediately in bilaterally nephrectomized Israeli dogs. Dr. Collins is currently the Director of Transplantation at Pacific Medical Center, San Francisco.

Dog Kidney Transport	
April, 1968	Los Angeles to San Diego
May	Los Angeles to Denver
June	Los Angeles to Boston
1969	
Sept. 15 &16	Los Angeles to London
Sept. 22,23,24	Los Angeles to Tel Aviv
Oct. 5 & 6	Los Angeles to Sydney
Oct. 22	Los Angeles to Portland
Oct. 30	Los Angeles to Salt Lake
Oct. 30	Los Angeles to Bethesda

Los Angeles to Israel Transplant

Dog No.	Days - Serum Creatinine mg%					
	1	2	3	4	5	6
1	2.2	1.6	1.7	1.6	1.5	1.2
2	2.0	2.4	2.0	1.6	1.6	
3	0.8	1.7	1.5	1.4		



It took many more years to convince surgeons to accept cold storage as a means of kidney preservation. Despite the fact that cold storage was almost 100 times cheaper than pulsatile pump perfusion, the complex machinery must have given most surgeons a sense of security. It was the French workers who first preserved a large series of human kidneys with Collins solution in 1972 (17) and demonstrated its effectiveness in human recipients. The use of simple cold storage spread throughout Europe but only gained acceptance in the United States gradually, as we documented in a series of papers (18,19). After publication of the first paper in 1970, it was 1976 before utilization of cold storage reached 30% of transplanted kidneys, and finally by 1985, the percentage reached the current levels of 85%.

Dr. Ramon Patel

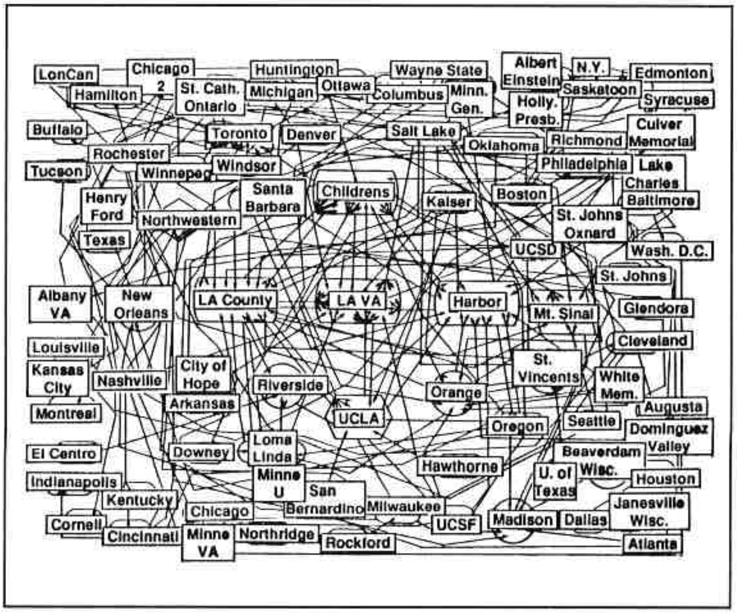
Finding a simple kidney preservation method was a bit of a crusade for us. It was disheartening to see such an extravagant expenditure in machines and personnel just to keep a kidney suitable for transplantation for 24 hours. Moreover, the machines made it very difficult to promote kidney sharing. Our NIH tissue typing contract was terminated in 1971 partly because we had diverted funds toward kidney preservation studies. This was a cause I felt had a vital connection to the application of tissue typing to transplantation. Perfecting the solution proved to be an extremely expensive endeavor, for toward the end of the project we had employed two surgeons, Drs. Collins and Shugarman; a full-time technician; and two full-time operating room nurses.

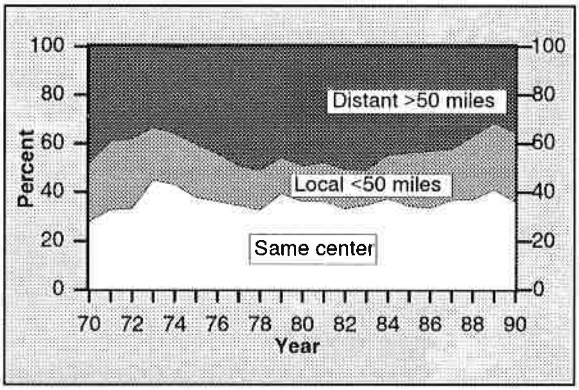
The Effect of Recipient Pool Size on the Incidence of Transplants Compatible for Five Major HLA Antigens

		No. of Potential Transplants Compatible	
ABO	No. of Donors	1-Hospital Pool	Both Kidneys in City Pool
O	31	19 (30.6%)	55 (88.7%)
A	11	2 (9.1%)	11 (50%)
B	8	4 (25%)	16 (100%)
AB	1	0 (0%)	0 (0%)
Total	51	25 (24.5%)	82 (80.4%)

The first citywide kidney sharing scheme in the United States was started in Los Angeles in 1967, as described by Dr. Patel (20). It was clear from the outset that we would have to share kidneys, even with tissue typing considerations aside. Often patients with the right ABO type were not available at the donor hospital, or a particular recipient was not available.

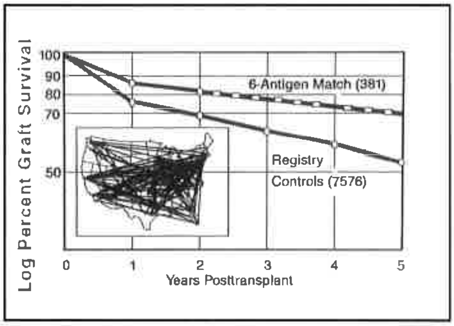
By 1971, a national listing of patients with their tissue types was developed with 864 waiting recipients from 61 centers. A total of 215 kidneys was exchanged (21). Kidney sharing had become part of the transplantation scene. Each arrow represents a kidney sent from a donating hospital (origin of arrow) to a recipient hospital (end of arrow).





Interestingly, the percentage of kidneys that was shared locally and for longer distances has remained almost constant for the past 20 years. The United Network for Organ Sharing (UNOS) was officially started in 1987, though no striking changes in the pattern of sharing kidneys is apparent. Kidneys have been shared not so much for matching as for various local "political" reasons throughout this time.

The culmination of cold storage and kidney sharing has finally occurred with the six-antigen-matched transplants. Since November 1987, by mutual agreement among all United States transplant centers, through UNOS, all potential donors were tissue typed and checked against all waiting recipients in the United States for a match. If a recipient with 6 HLA antigens matched was available, the agreement was to send that kidney to that recipient. To date, over 700 kidneys have been shipped under this agreement. The figure shows the outstanding results achieved by the six-antigen-matched kidneys compared to the controls. The map shows the distances that kidneys had to be shipped to achieve this result. Cold storage and tissue typing finally came together in this experience.

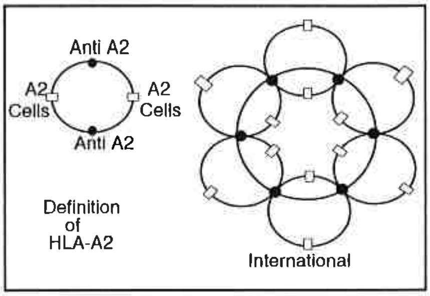


3) HLA TYPING

MAC	B_1	TER	LA_2	8^a
+	+			+
+	+	+	+	+
+	+	+		+
+	+	+		+
+	+	+	+	+
+	+	+		+
+	+	+		+
+	+	+		+
+	+	+	+	+
+	+	+		+
+	+	+	-	-
+	+	+	+	-
+	+	-		-
-	+	+		+
-	+	-	-	-
-	+			-
-	+		-	-
-	-	-		-
-	-			-
-	-	-		-
-	-		-	-
-	-	-		-
-	-	-		-
-	-	-		-
-	-	-		-
-	-	-		-
-	-	-	-	-
-	-	-		-
-	-	-	-	-
-	-	-	-	-
-	-	-	-	-
-	-	-	-	-

It was at the 1965 Second International Histocompatibility Workshop in Leiden, Holland that we first saw a concordance in HLA antigens defined by five different laboratories (listed horizontally): Dausset (MAC), Shulman (B_1), Terasaki (TER), Payne-Bodmer (LA_2), and Van Rood (8^a) (22). Among the cells tested (listed vertically), almost the same cells were independently classified by these five laboratories as being of a certain type. This then forms the basis for assigning a given HLA type. In this case the type was eventually named HLA-A2.

For the first 20 years of HLA testing, we were entirely dependent on antibodies to define a tissue type. These antibodies were defined by reference cells. As shown here, A2 is defined as the cell that reacts to anti-A2 antisera, and anti-A2 antisera are defined as sera that react with cells that are A2. Obviously we faced a severe element of circularity. Through international serum exchanges, we defined specificities not only by going in a circle but by going around in larger circles, tied to each other. There was no alternative in defining groups. The main consolation was that we were at least going around in the same circle as a result of the exchanges.



In 1970, our laboratory hosted the Fourth International Workshop - the first of the "Modern" Workshops, with Dr. Ekkehard Albert in charge of the analysis. It was the adoption of the microcytotoxicity test at this workshop that made the following possible: a) wide-scale sera exchanges; b) confirmation of HLA types; c) exchanges of antisera by mail; d) typing of many cells at different centers; and finally e) accumulation of results for a mass joint analysis. Dr. Albert returned to Munich, was subsequently in charge of the 1984 Ninth International Workshop, and is currently a Professor at the Laboratory of Immunogenetics in Munich.

Prof. Ekkehard Albert

After each workshop, the WHO Nomenclature Committee met and assigned new numbers to the new specificities identified and agreed upon by the exchange of sera. More than 100 specificities have accrued through the years. The need to exchange antisera and stay abreast of the newly defined antigens has kept the participants together. Tissue types determined anywhere in the world are standardized, thanks to the WHO Nomenclature Committee under the leadership of Sir Walter Bodmer.

International Workshops

Year	Site	Chairman	No. of new Ag	Total Ag
1. 1964	Durham, NC	Amos	-	
2. 1965	Leiden, Holland	Van Rood	-	
3. 1967	Torino, Italy	Ceppellini	9	9
4. 1970	Los Angeles, CA	Terasaki	17	26
5. 1972	Paris, France	Dausset	4	30
6. 1975	Aarhus, Denmark	Kissmeyer	16	46
7. 1977	Oxford, England	Bodmer	18	64
8. 1980	Los Angeles, CA	Terasaki	14	78
9. 1984	Munich, Germany	Albert	19	97
10. 1987	New York, NY	Dupont	19	106

It should be obvious by now that the antisera that define the specificities are the real key to HLA typing. We conceived of the idea of predispensing well-characterized antisera in microtrays for distribution to other laboratories so that each laboratory would only need to add lymphocytes to the common tray to obtain the HLA type. The data shown here are from one of the first experiments testing this concept.

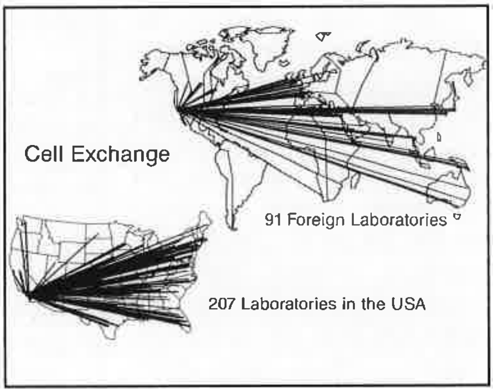
Lymphocytes were isolated from Dr. Donald Kuban, a trainee in our laboratory (who later was the first to find an HLA association with psoriasis), and sent around to various laboratories where our pre-dotted trays containing the horizontally listed antisera had previously been sent. The "1" denotes a negative reaction, and higher numbers show increasing strengths of positive reactions. The far right column shows that most of the labs were thus able to come to the same conclusion regarding the cell's type. The lymphocyte types are given in the older nomenclature: 8=B8, 9=B12, 6=Bw6.

Uniformity of Typing December 4, 1969

Cells - Kuban

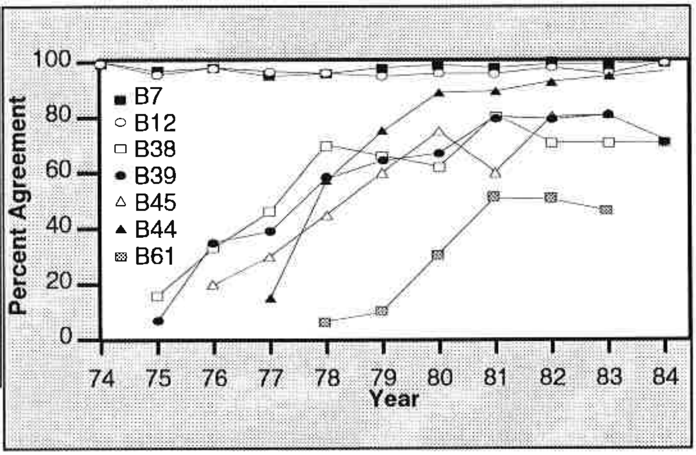
	Groups Second Sublocus							Lymphocyte Types
Center	5	7	8	9	10	11	6	
UCLA	1111	1111	8888	6888	1411	111	646	896
Boston	1111	1111	8868	6666	1622	116	641	896
Cleveland	1111	1111	8888	6888	1211	116	668	896
Detroit	1111	1111	6666	6666	1212	116	666	896
Houston	1111	1111	8888	6888	1611	111	866	896
Kansas	1111	1112	8888	8888	1616	111	888	896
Center X	1111	1111	2628	1111	1111	111	111	8
Toronto	1111	1111	8888	8118	1111	111	888	896
Salt Lake City	1111	1111	8888	8688	1441	111	868	896
Cincinnati	1111	1111	8888	6668	1111	111	616	896
Mayo Clinic	1111	1111	8888	8828	2421	111	626	896
San Diego	1111	1111	8888	8888	1412	111	828	896
Milwaukee	1111	1111	8888	6868	1111	111	428	896
Buffalo	1444	1116	8888	8611	1114	111	666	896
Montreal	1111	1111	8868	4888	1111	111	446	896
Nashville	1111	1042	8888	6882	1212	122	886	896

When our NIH contract was terminated, we sold trays from the UCLA Tissue Typing Laboratory for a 14-year period (1970 to 1984). During that time, most of the transplants performed in the United States and Canada were typed using these trays. Since 1984 the common tray has been produced by the same crew of former UCLA technicians at a company called One Lambda. It is estimated that more than half of the transplants performed in the United States are still typed using these trays.



Another important complimentary way in which HLA antigens were standardized, in addition to the histocompatibility workshops where the same sera were tested, was by many laboratories typing the same cells with their own sera. This was accomplished by shipping cells from four persons to laboratories throughout the world on a monthly basis. This type of testing became possible after our development of a solution for the room temperature preservation of lymphocytes by Dr. Park (23). We have sent out sets of four cells on a continuous monthly basis for the past 16 years (24). Current participation in the International Cell Exchange has increased to 298 laboratories that voluntarily submit to this blind test in order to monitor their ability to identify the various HLA antigens and to compare their results to those of other laboratories. With international uniformity, the international exchange of organs and bone marrow is now a reality.

Prof. Min Sik Park



Some examples of progress in the definition of antigens are shown here. B38 and B39, which were barely identified by 10% of the labs in 1975, were subsequently detected by an increasing number of labs until by 1984, they were detected by 70% of the labs. Other antigens such as B7 and B12 have been detected by over 95% of the labs since 1975.

The cell exchange has documented the accuracy of HLA typing worldwide over a 16-year period. It is important to note that as we sought to use tissue typing for clinical transplants, definition of the HLA specificities was still being developed. For example, of the transplants performed in 1975, very few could be expected to have been typed for B38 and B39. Even today, there are some specificities that are very well defined and others that are developing. We have seen that the inability to detect specificities is generally not attributable to the skill of the tissue typer, but rather to the availability of good antisera. In fact, the history of HLA typing has been the constant drive to find better antisera that define the types. Sera that react strongly (and are therefore prone to less technical errors) are rare. So too are sera that define the esoteric types that are difficult to identify.

4) CROSSMATCH

The first case of hyperacute rejection with a positive lymphocyte cytotoxicity crossmatch test was described in 1964 (25). A transplant was performed by Dr. Goodwin from a brother to his sister, who was the mother of a child. The operation, which was demonstrated on closed circuit TV for a meeting in Los Angeles, was technically successful, but the living-donor kidney was completely without function. Two years later, two additional cases of hyperacute rejection with a positive crossmatch using leukoagglutination tests were described by Kissmeyer-Nielsen (26).

Immediate Rejection							
Sex	F	F	F	M	F	F	F
Center	UCLA	Adelaide	Richmond	Boston	Cleveland	UCLA	Richmond
Pregnancies	1	2	3	-	5	2	0
Donor	+	+		+		+	+
Husband	+	+	+		+	+	+

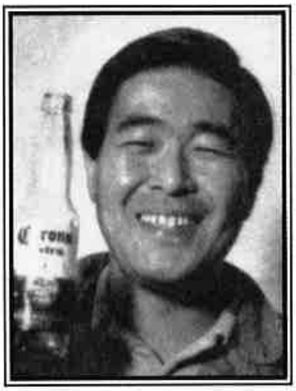
At the Paris International Transplant Society meeting in 1967, we presented seven cases of hyperacute rejection which had been identified retrospectively (27). Significantly, six of seven cases occurred in women, and five in women with previous pregnancies. This was exactly the situation in which preformed antibodies might be suspected. The antibodies were found to react to cells of the husband. Prospective use of crossmatching was only begun after 24 of 30 cases of a positive lymphocyte cytotoxicity crossmatch were retrospectively shown to be associated with hyperacute rejection by Patel, et al in 1969 (28), and evidence developed from other studies (29).

Prof. Peter Morris

Peter Morris, working in our lab, showed that cytotoxic antibodies occur in the serum of patients who have rejected kidney transplants (30). This finding fit well with the observation that hyperacute rejections were more often observed in regrafted patients. Morris was later to become Professor of Surgery at Oxford and to send his student, Alan Ting, to work in our laboratory.

Although the standard crossmatch test is performed today in essentially the same way as it was introduced in 1964, there was a need to make the crossmatch test more sensitive. Dr. Alan Ting investigated various methods and came to the conclusion that the easiest method would be to simply increase the incubation time (31). This so-called "long" test is used in many laboratories today. Antiglobulin tests have also been an important modification (32). Some antibodies were not clinically relevant. Dr. Robert Ettenger, working in our lab, showed that positive crossmatch tests in which B- but not T-donor lymphocyte cells were the antibody target did not result in hyperacute rejection (33). Additionally, IgM antibodies were shown to be innocuous by George Ayoub (34).

Dr. Alan Ting



Prof. Yuichi Iwaki

As demonstrated by Dr. Yuichi Iwaki, the problem of false positive crossmatch tests was often due to autoantibodies that were reactive in the cold (35). We had shown earlier that these autocytotoxic antibodies were present in infectious mononucleosis, pregnancies (36), various infections (37), and systemic lupus erythematosus (38). Iwaki went further to show that the failure of many kidneys to function was probably attributable to unrecognized hyperacute rejection (39). He is now Professor and Director of the Histocompatibility Laboratory at the University of Pittsburgh.

Dr. Daniel Cook

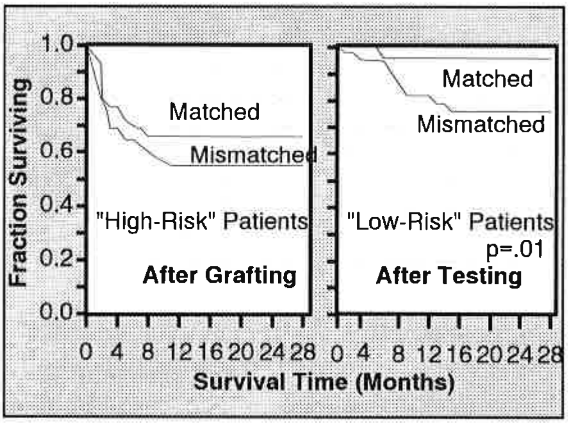
Crossmatching by flow cytometry, first introduced by Garovoy (40), was shown to have relatively little effect on first transplants, but Cook in our laboratory demonstrated a strong effect on regrafts (41). Use of platelets for crossmatching has also been useful. We now have evidence from large numbers of transplants that even first graft survival is influenced by flow cytometry crossmatching. Dr. Cook is now Director of the Histocompatibility Laboratory at the Medical College of Virginia.

5) HISTOCOMPATIBILITY

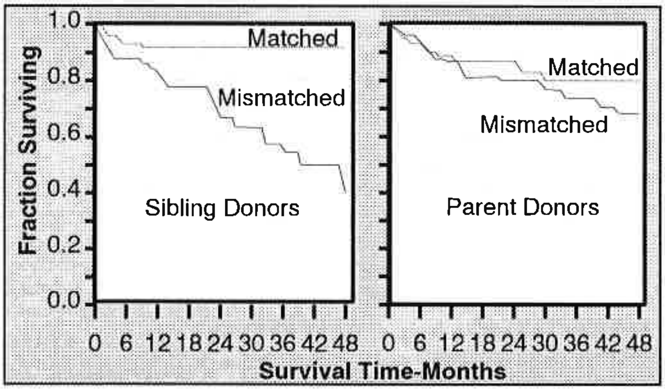
Prof. Thomas E. Starzl

Early in 1964, Dr. Thomas Starzl began to supply us with blood from donors and recipients from his now classical series of transplants. The first studies with his kidney transplant patients were published in "*Histocompatibility Testing*" in 1964 (25). Shortly thereafter, the first attempt to use tissue typing for donor selection for transplantation was also done with Starzl in 1966 (42). The early work in tissue typing of kidney transplant patients was based to a large extent on the patients supplied by Dr. Starzl. We are indebted to him for his continued support for the past 25 years.

By 1967, 196 kidney transplant patients and their donors from nine transplant centers were typed and reported at the Santa Barbara Transplant Meeting (13). The subsequent follow-up survival comparison among the retrospectively typed pairs was clearly different for matched and mismatched transplant pairs. This was the first indication that tissue matching might improve clinical kidney transplant outcome.



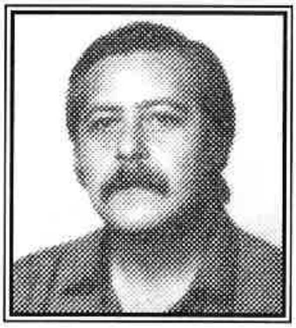
Prof. D.P. Singal



Dr. D.P. Singal, working in our lab, showed for the first time that HLA typing could separate the matched and mismatched sibling-donor transplants extremely well (43). This was the first demonstration that HLA-identical sibling grafts had a higher survival rate than mismatched grafts.

Transplants from parental donors had the same survival rate, whether they were matched or mismatched. To this day, 20 years later, HLA matching has not been very useful in determining which parent is a more suitable donor.

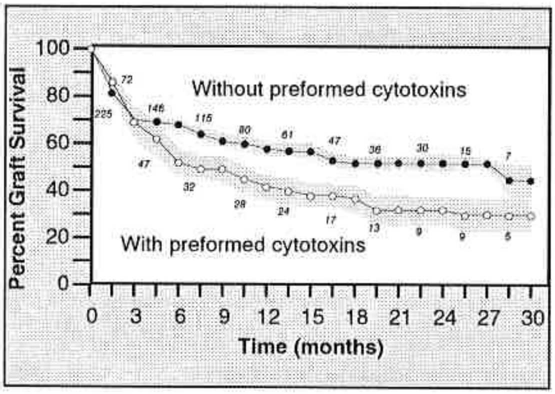
This slide was shown at the 1970 International Transplant meeting at the Hague with Lego blocks appropriated from the kids. Clinical rank of the patients from A to F and N (meaning nonimmunologic failure) is shown along the horizontal axis. The vertical axis shows the degree of matching from the best A match to the worst D match. The few transplants with excellent matches did well. However, the most disturbing feature was the large number of patients who did well despite being mismatched (14). This same problem exists today, even though 70 HLA A,B, and DR specificities have been used in comparison to the 11 HLA-A,B types known in 1970.



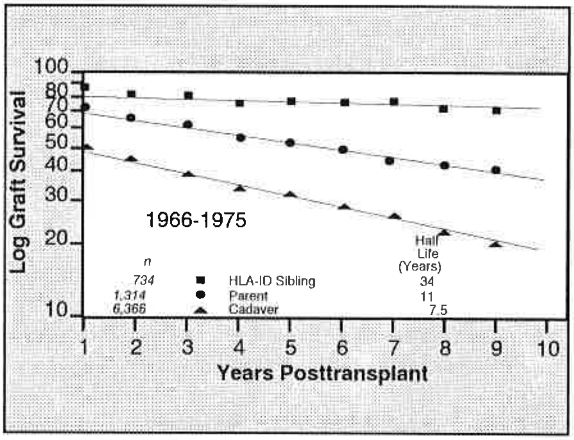
Prof. Miguel Kreisler

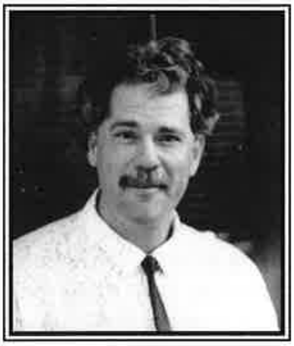
Since everyone had expected tissue match and outcome to be correlated, there was much disappointment in and criticism of our studies. Within two months we were site visited, and the NIH contract was discontinued. A special meeting was called within four months of the Hague meeting by Dausset and Rapaport in Paris, where tissue typing data from all the international labs was accumulated (44). The results again showed no correlation of HLA matching with cadaveric transplant outcome, and the results were never published.

In trying to explain the lack of correlation between matching and outcome, we turned to an examination of the sensitization status of the recipients with Dr. Miguel Kreisler, now Professor of Immunology in Madrid. This study was the first to introduce the concept of panel reactive antibodies (PRA) as a measure of sensitization (45). The cytotoxicity of the serum of a patient against a random panel of donors showed the degree of preimmunization present in the recipient. Patients who were not sensitized had a higher graft survival than those who were sensitized. Interestingly, this measure of humoral immunity still remains today, 20 years later, as essentially the only practical measure of sensitization. Means of detecting cellular sensitization remain elusive.

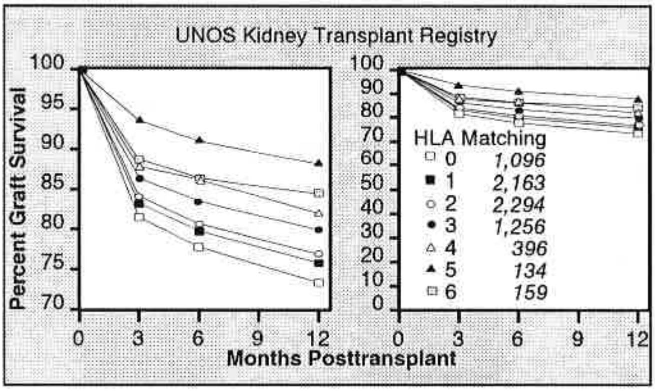


In 1978, after 15 years of HLA typing, the editors of Vox Sang put together a summary by eight authors. We submitted this figure, showing that long-term graft survival was strongly influenced by the number of HLA haplotypes which were mismatched and that the *rate* of failure was constant for each type of transplant (46). The late loss rate expressed as half-life has remained the same throughout the past 25 years (47). In other words, regardless of improvements in immunosuppression, the long-term loss rate has remained unchanged.

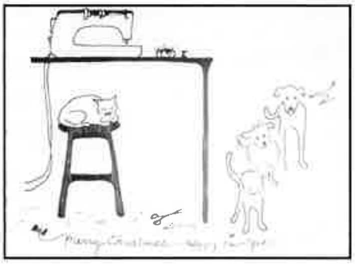


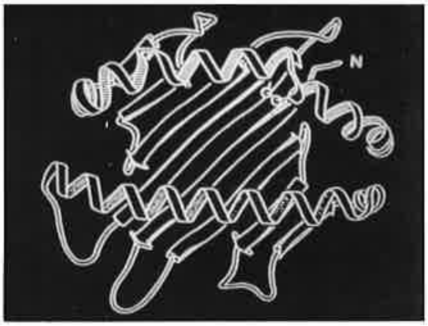


Dr. James Cicciarelli



Matching cadaver donors and recipients for the HLA A,B,DR antigens known today results in some correlation with outcome, as shown by Cicciarelli, et al (48). Transplants with fewer numbers of mismatched antigens have higher graft survival than those with larger numbers of mismatch. The data shown in the left and right hand graphs are the same; except that the vertical axis goes down to 70% in the left hand graph and down to 0% in the right hand one. The left hand figure depicts how the data are often plotted by tissue typers and the right hand method is used by surgeons. On the one hand, there is a large difference, on the other hand, the difference exists but is smaller in magnitude.


Merry Christmas — Happy New Year

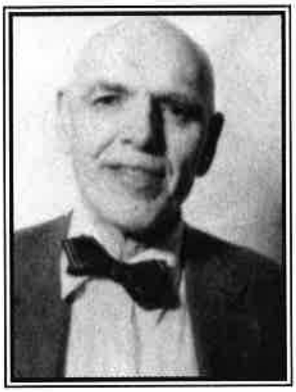


Probably the last chapter on histocompatibility matching remains to be written. Recent studies by Bjorkman, Strominger, et al (49) have shown the actual molecular structure of HLA to be as shown here. This major achievement tells us more precisely what it is the antibodies are reacting to and what the immune cells have to deal with.

As a result of the efforts of many molecular biologists, the exact sequence of amino acids that comprise the HLA molecules is now being established. From this detailed knowledge we hope to construct a new matching system for transplantation. Since the basic units of difference that exist between the recipient and the donor are the amino acids, we need only know which ones are of consequence. We used the computer to chop the molecule into amino acid peptides of varying lengths (50). Our current task is to determine how these peptides or the tertiary structure of the epitopes can be used to match.

	61 D	62 R	63 E	64 T	65 Q	66 I	67 V	68 K	69 A	70 Q	71 S	72 Q	73 T	74 D	75 R	76 E	77 S
A1	-	Q	-	-	R	N	M	-	-	H	-	-	-	-	-	A	N
A2	-	G	-	-	R	K	-	-	-	H	-	-	-	H	-	V	D
A3	-	Q	-	-	R	N	-	-	-	-	-	-	-	-	-	V	D
A11	-	Q	-	-	R	N	-	-	-	-	-	-	-	-	-	V	D
A24	-	E	-	-	R	K	-	-	-	H	-	-	-	-	-	-	N
A25	-	-	N	-	R	N	-	-	-	H	-	-	-	-	-	-	-
A26	-	-	N	-	R	N	-	-	-	H	-	-	-	-	-	A	N
A29	-	L	Q	-	R	N	-	-	-	-	-	-	-	-	-	A	N
A30	-	Q	-	-	R	N	-	-	-	-	-	-		-	-	V	D
A31	-	Q	-	-	R	N	-	-	-	H	-	-	I	-	-	V	D

6) THE KIDNEY TRANSPLANT REGISTRY


Dr. Ray Mickey

From the outset, we realized it would be impossible to get answers to the question of the efficacy of histocompatibility matching by testing patients from only one center. Dr. Ray Mickey supplied the statistical help we needed so badly, and we have enjoyed his collaboration for over 25 years. Despite retirement he continues to consult on this project. By the time we reported at the 1970 Hague meeting, we had typed transplants with the collaboration of 54 centers (14). Since there was no resolution of the problem even then, we decided to gather data on other factors that might be confounding the results of histocompatibility. Thus, the UCLA Kidney Transplant Registry was begun in 1969 and currently collects data from over 200 centers. Beverly Graver was in charge of the registry file for 22 years and works part time since her retirement early in 1991.

Prof. Gerhard Opelz

Gerhard Opelz was another valuable contributor in the first 10 years. He was instrumental in identifying factors such as center (51), race (52), and regraft (53) effects. One of the important factors he had noted was the paradoxical effect of transfusions (54). Unfortunately, in recent data, this effect has diminished considerably. Dr. Opelz has continued accumulating data internationally since 1982 from his new base at the University of Heidelberg, where he is Professor of Immunology.

Dr. Michael Cecka

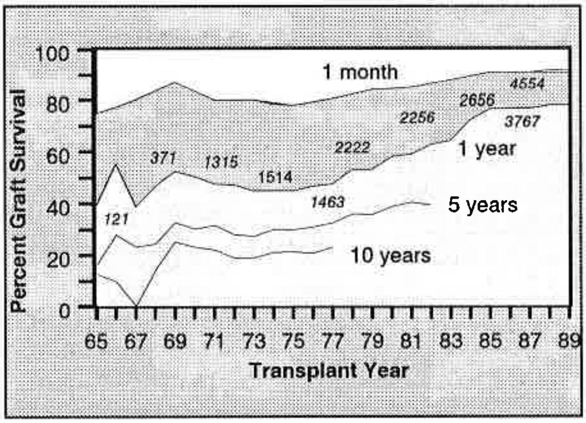
Dr. Yong Cho

With voluntary contributions from over 200 transplant centers, the number of patients in the registry rose steadily, until today it contains the results from 100,000 transplants. The recent addition of the UNOS Transplant Registry data gathered in our laboratory under a UNOS contract with Dr. Michael Cecka as the registry manager, brings the total data collected to over 125,000 transplants. The registry information helped us learn considerably more about the factors that influence transplants (55). Dr. Yong Cho has supplied invaluable computer programming and statistical analysis for the past 12 years.

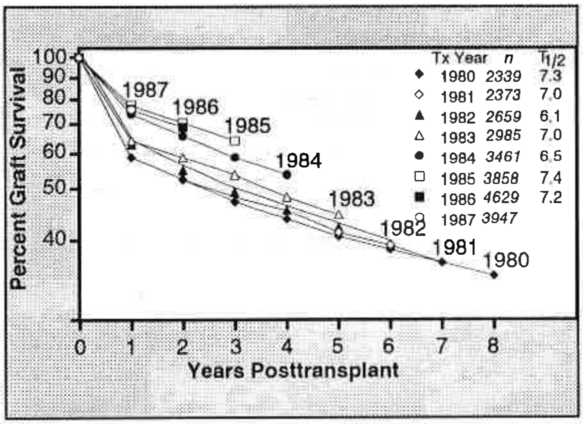
Worldwide Transplant Center Directory

	No. of Centers	No. of Patients	
		1990	Total
Kidney	488	21,590	234,559
Bone marrow	261	6,257	39,634
Heart	214	3,522	16,136
Liver	135	3,604	14,168
Pancreas	118	647	2,836
Lung	62	347	793

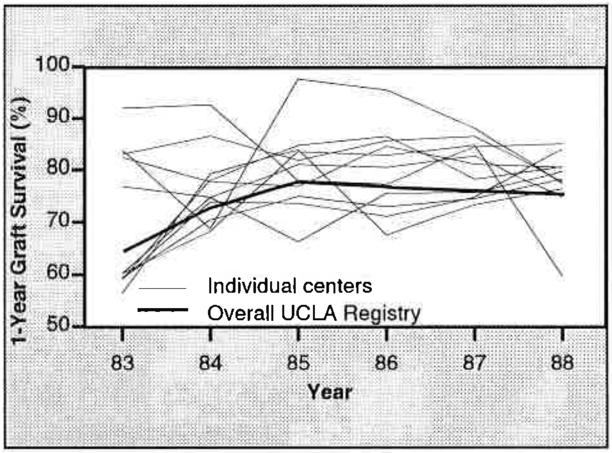
Beginning in 1985 and annually through 1990, we have published Registry results in our *Clinical Transplants series*. The worldwide directory totals for these organ transplants were recently obtained from data supplied from the transplant centers. In addition, these volumes contain the results from excellent large centers for comparison with registry results.



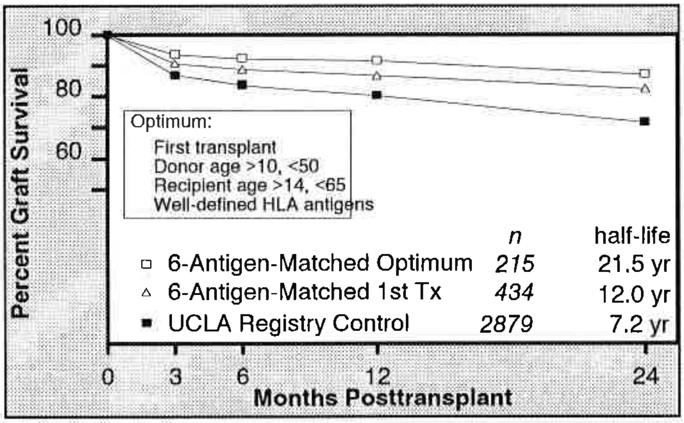
The ability to monitor changes over time represents one of the most important types of data to emerge from the registry. Note the trends in graft survival rates over the years. Initially, there was a long period when graft survival rates did not improve and, in fact, even declined until 1975. Since then, there has been a steady rise which reached a plateau in the past five years. With the introduction of cyclosporine and the initial spurt of improvement in survival, we have reached another period of impasse. This type of trend study is made possible only by the continuous collection of data from the transplant centers (56).



The steady long-term loss in transplants over a 10-year period is apparent. Moreover, despite the fact that one-year graft survival has improved, the long-term loss rate remains the same among transplants performed in each succeeding time period (47). The principal challenge presently facing the transplant community is improvement of long-term survival rates. Though 80% survival at one year is a significant surgical accomplishment, from the patient's point of view, such low 10-year survival can be quite discouraging. For a 20-year-old recipient to reach the age of 60 with a functioning kidney would require four or more transplants.



Another important registry role has been the creation of a broad canvas to permit viewing of the forest, rather than the trees. As shown here, the graft survival at different transplant centers varied greatly. The thick line shows the overall trend, whereas the thin lines show the results at each of the larger centers. Because of the limited number of transplants that could be performed at each center and the many variables that influence the results, the outcome was often variable. There were good and bad years at each center and, consequently, times to publish and times not to publish. Thus by reading the reports, it was difficult to see the forest. The registry served to bring all the multifactorial data together into one mass, which, surprisingly, was quite stable. We came to know that all along we had been doing the now well-accepted type of analysis called meta analysis.



Steve Takemoto

Steve Takemoto has carefully monitored the success of the six-antigen-matched transplant program through a series of questionnaires. Despite the great variation of results at different centers, as evidenced by the one-year graft survivals, Takemoto, et al showed that if kidneys came from six-HLA antigen-matched donors, the graft survival was as high as at the very best centers. This occurred despite the fact that the kidneys were harvested at 227 centers and transplanted at 175 centers with varying degrees of experience. Thus, HLA-matched kidneys have overcome the center effect as well as the adverse influence of longer cold ischemia times (57). It has therefore become clear that HLA typing is sufficiently accurate and standardized so that donors and recipients typed at over 100 different centers could be matched. Now it can be said that the major antigens are being identified by the tissue typing laboratories to achieve results comparable to those of HLA-identical siblings.

Barbara Schulman and Roger Smith

From the first interhospital sharing (20) in Los Angeles, the Southern California Regional Organ Procurement Agency (ROPA) was formed. Roger Smith and Barbara Schulman have been the mainstays of this organization based at our laboratory for the past 15 years. They represent a cadre of unsung transplant coordinators throughout the United States who are responsible for coordinating the surgical, tissue typing, and distribution teams. Slightly over 500 cadaver donor kidney transplants are performed each year in Los Angeles.

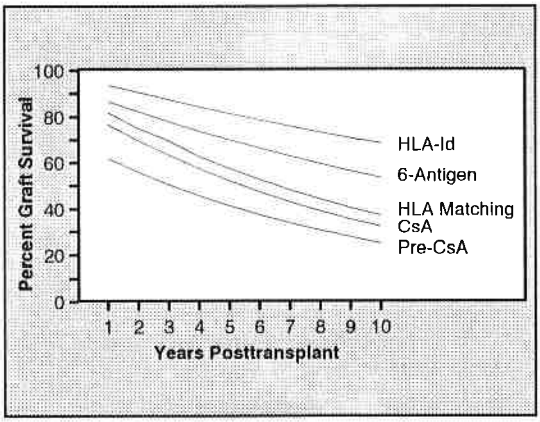
One of the newer findings from the registry was that IgA nephropathy patients have an unusually high graft survival rate as described by Dr. Eduardo Lim (58). IgA antibodies directed against HLA have been found by Dr. David Chia, suggesting that these noncomplement-fixing antibodies may interfere with the cytotoxic ones, thus acting as blocking antibodies, as in previous studies (59).

Dr. David Chia

Dr. David Gjertson

Although HLA matching was questioned as having only a minor effect even if adopted nationally (60), Gjertson recently presented data showing that the long-term gains produced by cyclosporine and the potential gains to be expected from a national matching policy would result in about the same magnitude of gain at 10 years, ie, 7% for cyclosporine and 5% for matching (61). This is the basis upon which we advocate the use of HLA matching as the primary factor in national kidney allocation. In fact, when I was honored to be elected President of the International Transplant Society in 1983, my theme was International sharing of organs for all of mankind (62).

Today, after 27 years of trying to utilize tissue typing for kidney transplant patients, allocation of organs by tissue typing remains controversial. We have faith, however, that eventually HLA epitope matching will lead to more transplants being performed that require less immunosuppression. Stronger and stronger drugs may not be the only answer after all.



REFERENCES

1. Longmire WP, Stone HB, Daniel AS, et al. Report of clinical experiences with homografts. Plast Reconstr Surg 1947; 2:419.
2. Cannon JA, Longmire WP Jr. Studies of successful skin homografts in the chicken. Ann Surg 1952; 135:60.
3. Billingham R, Brent L, Medawar P. Quantitative studies on tisue transplantation immunity. III. Actively acquired tolerance. Philos Trans R Soc Lond (Bid) 1956; 239:357.
4. Terasaki PI, Cannon JA, Longmire WP Jr. Mortality of chick embryos upon injection of homologous adult cells. Proc Soc Exp Biol Med 1959; 100:639.
5. Medawar PB. The use of antigenic tissue extracts to weaken the immunological reaction against skin homografts in mice. Transplantation 1963; 1:21.
6. Terasaki PI, Cannon JA, Longmire WP Jr. Antibody response to homografts. 1. The technic of lymphoagglutination and the detection of lymphoagglutinins upon spleen injection. Proc Soc Exp Biol Med 1959; 102:280.
7. Terasaki PI, McClelland JD, Cannon JA, Longmire WP Jr. Antibody response to homografts. VII. The role of complement in cytotoxicity of serum from homografted rabbits. J Immunol 1961; 87:39.
8. Terasaki PI, McClelland JD. Antibody response to homografts. VIII. Relation of mouse hemagglutinins and cytotoxins. J Exp Med 1963; 117:675.
9. Terasaki PI, McClelland JD. Microdroplet assay of human serum cytotoxins. Nature 1964; 204:998.
10. Mittal KK, Mickey MR, Singal DP, Terasaki PI. Serotyping for homotransplantation XVIII. Refinement of microdroplet lymphocyte cytotoxicity test. Transplantation 1968; 6:913.
11. Terasaki PI, Bernoco D, Park MS, et al. Microdroplet testing for HLA-A,-B,-C, and -D antigens. Am J Clin Pathol 1978; 69:103.
12. Terasaki PI. History of HLA: A personalized view. In: Terasaki PI, Ed. History of HLA:Ten Recollections. Los Angeles, UCLA Tissue Typing Laboratory, 1990; 213.
13. Terasaki PI, Vredevoe DL, Mickey MR. Serotyping for homotransplantation. X. Survival of 196 grafted kidneys subsequent to typing. Transplantation 1967; 5:1057.
14. Mickey MR, Kreisler M, Albert ED, et al. Analysis of HLA incompatibility in human renal transplants. Tissue Antigens 1971; 2:57.
15. Collins GM, Bravo-Shugarman M, Terasaki PI. Kidney preservation for transportation: Initial perfusion and 30 hours ice storage. Lancet 1969; 2:1219.
16. Collins GM, Bravo-Shugarman M, Terasaki PI, et al. Kidney preservation for transport. IV. Eight-thousand-mile international air transport. Aust NZ J Surg 1970; 40:195.
17. Collaborative Study from Four Paris Hospitals. Lancet 1972; 2:887.
18. Clark EA, Opelz G, Mickey MR, Terasaki PI. Evaluation of Belzer and Collins kidney preservation methods. Lancet 1973; 1:361.
19. Opelz G, Terasaki PI. Kidney preservation: perfusion versus cold storage-1975. Transplant Proc 1976; 8:121.
20. Patel R, Glassock R, Terasaki PI. Serotyping for homotransplantation. XIX. Experience with an interhospital scheme of cadaver kidney sharing and tissue typing. JAMA 1969; 207:1319.
21. Terasaki PI, Wilkinson G, McClelland J. National transplant communications network. JAMA 1971; 218:1674.

22. Terasaki PI, Vredevoe DL, McClelland JD. Serotyping for homotransplantation VI: use of cryogenically stored cells for purification of antisera. In: Amos DB, van Rood JJ, Eds. Histocompatibility Testing 1965; Baltimore, Williams & Wilkins, 1966; 267.

23. Park MD, Terasaki PI. Storage of human lymphocytes at room temperature. Transplantation 1974; 18:520.

24. Lau M, Terasaki PI, Park MS, Barbetti A. Fifteen-year overview of the International Cell Exchange. In: Terasaki PI, Ed. Clinical Transplants 1989. Los Angeles, UCLA Tissue Typing Laboratory, 1989; 447.

25. Terasaki PI, Marchioro TL, Starzl TE. Serotyping of human lymphocyte antigens. Preliminary trials on long-term kidney homograft survivors. Natl Acad Sci-monograph on histocompatibility testing, Washington, DC, 1965; 83.

26. Kissmeyer-Nielsen F, Steen F, Olsen F, et al. Hyperacute rejection of kidney allografts, associated with pre-existing humoral antibodies against donor cells. Lancet 1966; 2:662.

27. Terasaki PI, Thrasher DL, Hauber TH. Serotyping for homotransplantation. XIII. Immediate kidney transplant rejection and associated preformed antibodies. In: Dausset J, Hamburger J, Mathe G, Eds. Advance in Transplantation. Baltimore, Williams and Wilkins, 1967; 225.

28. Patel R, Terasaki PI. Significance of the positive crossmatch test in kidney transplantation. N Engl J Med 1969; 280:735.

29. Starzl TE, Lerner RA, Dixon FJ, et al. Schwartzman reaction after human renal homotransplantation. N Engl J Med 1968; 278:642.

30. Morris, PJ, Mickey MR, Singal DP, Terasaki PI. Serotyping for homotransplantation XXII. Specificity of cytotoxic antibodies developing after renal transplantation. Br Med J 1969; 1:758.

31. Ting A, Hasegawa T, Ferrone S, Reisfeld RA. Presensitization detected by sensitive crossmatch tests. Transplant Proc 1973; 5:813.

32. Fuller TC, Cosimi AB, Russell PS. Use of antiglobulin ATG reagent for detection of low levels of alloantibody-improvement of allograft survival in presensitized recipients. Transplant Proc 1978; 10:463.

33. Ettenger RB, Terasaki PI, Ting A, et al. Anti-B lymphocytotoxins in renal allograft rejection. N Engl J Med 1976; 295:305.

34. Ayoub G, Terasaki PI, Iwaki Y, Park MS. Presensitization tests for potential transplant recipients. Dial Transplant 1978; 7:496.

35. Iwaki Y, Lau M, Terasaki PI. Successful transplants across T warm-positive crossmatches due to IgM antibodies. Clin Transplant 1988; 2:81.

36. Naito S, Mickey MR, Hirata AA, Terasaki PI. Autolymphocytotoxins following immunization by pregnancies, transplantation, and disease. Tissue Antigens 1971; 1:219.

37. Kreisler M, Naito S, Terasaki PI. Cytotoxins in disease. V. Various diseases. Transplant Proc 1971; 3:112.

38. Terasaki PI, Mottironi VD, Barnett EV. Cytotoxins in disease. Autocytotoxins in lupus. N Engl J Med 1970; 283:724.

39. Iwaki Y, Terasaki PI. Primary nonfunction in human cadaver kidney transplantation:evidence for hidden hyperacute rejection. Clin Transplant 1987; 1:125.

40. Garovoy MR, Rheinschmidt MA, Bigos M, et al. Flow cytometry analysis: a high technology crossmatch technique facilitating transplantation. Transplant Proc 1985; 17:693.

41. Cook DJ, Terasaki PI, Iwaki Y, et al. An approach to reducing early kidney transplant failure by flow cytometry crossmatching. Clin Transplant 1987; 1 (5):253.

42. Terasaki PI, Porter KA, Marchioro TL, et al. Serotyping for homotransplantation. VII. Selection of kidney donors for thirty-two recipients. Ann NY Acad Sci 1966; 129:500.

43. Singal DP, Mickey MR, Terasaki PI. Serotyping for homotransplantation. XXIII. Analysis of kidney transplants from parental versus sibling donors. Transplantation 1969; 7:246.

44. Dausset J, Rapaport FT. The role of histocompatibility typing in clinical organ transplantation: An International Symposium. Transplant Proc 1971; 3: No.2.

45. Terasaki PI, Mickey MR, Kreisler M. Presensitization and kidney transplant failures. Postgrad Med J 1971; 47:89.

46. Terasaki PI, Opelz G. Fifteen years of HLA: Which is the importance of HLA compatibility for the clinical outcome of renal transplantation? Vox Sang 1978; 34:184.

47. Terasaki PI, Mickey MR, Iwaki Y, et al. Long-term survival of kidney grafts. Transplant Proc 1989; 21:615.

48. Cicciarelli J, Terasaki PI. Matching cadaver transplants achieve graft survivals comparable to living related transplants. Transplantation Proc 1991; 23:1284.

49. Bjorkman PJ, Saper MA, Samraoui B, et al. The foreign antigen binding site and T cell recognition regions of Class I histocompatibility antigens. Nature 1987; 329:512.

50. Takemoto S, Terasaki PI. HLA peptide matching. In: Terasaki PI, Ed. Clinical Transplants 1990. Los Angeles, UCLA Tissue Typing Laboratory, 1991; 497.

51. Opelz G, Mickey MR, Terasaki PI. HLA matching and cadaver kidney transplant survival in North America: influence of center variation and presensitization. Transplantation 1977; 23:490.

52. Opelz G, Mickey MR, Terasaki PI. Influence of race on kidney transplant survival. Transplant Proc 1977; 9:137.

53. Opelz G, Mickey MR, Terasaki PI. Prolonged survival of second human kidney transplants. Science 1972; 178:617.

54. Opelz G, Sengar DPS, Mickey MR, Terasaki PI. Effect of blood transfusions on subsequent kidney transplants. Transplant Proc 1973; 4:253.

55. Cecka JM, Terasaki PI. The UNOS Scientific Transplant Registry-1990. In: Terasaki PI, Ed. Clinical Transplants 1990. Los Angeles, UCLA Tissue Typing Laboratory, 1991; 1.

56. Terasaki PI, Cecka JM, Takemoto S, et al. Overview. In: Terasaki PI, Ed. Clinical Transplants 1988; Los Angeles, UCLA Tissue Typing Laboratory 1988, p 409.

57. Takemoto S, Carnahan E, Terasaki PI. Report on 604 six-antigen-matched transplants. In: Terasaki PI, Ed. Clinical Transplants 1990. Los Angeles, UCLA Tissue Typing Laboratory, 1990; 485.

58. LIm, EC, Terasaki, PI. Outcomes of kidney transplants in different diseases. In: Terasaki PI, Ed. Clinical Transplant 1990; Los Angeles, UCLA Tissue Typing Laboratory, 1991; 461.

59. Chia, D, Horimi, T, Terasaki, PI, Hermes, M. Association of anti-Fal and anti-IgG antibodies with higher kidney transplant survival. Transplant Proc 1982; 14:322.

60. Held PJ, Kahan B, Hunsicker LG, et al. The impact of HLA mismatches on kidney graft survival. Presented at the Sixteenth Annual Scientific Meeting of the American Society of Transplant Surgeons, Chicago, Illinois; May 30 - June 1, 1990.

61. Gjertson DW, Terasaki PI, Takemoto S, Mickey MR. National allocation of cadaveric kidneys by HLA matching: Projected effect on outcome and costs. N Engl J Med 1991; 324:1032.

62. Terasaki PI. Presidential address: Transplantation Society, 1982. Transplant Proc 1983; 15:1202.

CURRICULUM VITAE

Paul I. Terasaki

PERSONAL

Born: September 10, 1929, Los Angeles, California; Married, 4 children

Address: UCLA Tissue Typing Laboratory
950 Veteran Avenue, Los Angeles, CA 90024
TEL: (213) 825-7651, FAX: (213) 206-3216

EDUCATION

1945	Gila River Camp High School, Arizona
1946	Hyde Park High School, Chicago
1948	A.A. - University of Illinois
1950	B.A. - University of California, Los Angeles
1952	M.A. - University of California, Los Angeles
1956	Ph.D. - University of California, Los Angeles

POSITIONS

1955-56	Junior Research Zoologist, Department of Surgery, UCLA
1957-58	Postdoctoral Research Fellow, USPH Department of Zoology, University College London, with P.B. Medawar
1958-61	Assistant Research Zoologist, Department of Surgery, UCLA
1961-63	Associate Professor of Surgery-in-Residence, Department of Surgery, UCLA
1963-69	Professor of Surgery-in-Residence, Department of Surgery, UCLA
1973-	Director, Southern California Regional Organ Procurement Agency
1969-	Director, UCLA Tissue Typing Laboratory
1969-	Professor of Surgery, Department of Surgery, UCLA

MEMBERSHIPS

1968-	World Health Organization: Nomenclature Committee for Leukocyte Antigens	
1967-70	National Institute of Allergy and Infectious Diseases: Transplantation and Immunology Committee	
1980-84	American Society of Transplant Physicians	
	American Society of Transplant Surgeons (Honorary Member)	
1972-78	Councillor, International Transplantation Society	
1982-84	President, International Transplantation Society	
1970-89	International Histocompatibility Society	
	1970	Secretary
	1970-72	President
	1978-80	Secretary
	1980-84	President

1988-89	President, American Society of Histocompatibility and Immunogenetics
1987-89	United Network for Organ Sharing (UNOS) Histocompatibility Committee

1987	Director, National Kidney Transplant Registry
1987	Scientific Advisory Committee
1989	Board of Directors

JOURNAL EDITORIAL BOARDS

Transplantation
Clinical Nephrology
Immunogenetics
Transplantation Proceedings
Human Immunology
Contemporary Nephrology

AWARDS

1970	Netherlands Red Cross Medal
1971	Modern Medicine Award for Distinguished Achievement
1973	UCLA Alumni Distinguished Achievement Award
1977	American Society of Clinical Pathologists: Philip Levine Award
1988	American Society of Histocompatibility and Immunogentics: Rose Payne Award
1991	Karl Landsteiner Award, American Association of Blood Banks

PUBLICATIONS

Total: 750

Citations (from the Scientist)

1965-78	rank #55	7,379
1973-84	rank #61	8,506

RECOLLECTION

Fritz Bach

Address: Immunobiology Research Center
Box 724 Mayo Memorial Building
University of Minnesota
Minneapolis, Minnesota 55455

Fritz Bach

RECOLLECTION

Fritz Bach

My fascination with transplantation dates back to my years as a student at Harvard. I was fortunate enough to be in Boston when Hume, Murray, and their colleagues performed their pioneering studies in transplantation, including the first United States attempt at kidney allotransplantation. It was just a few years later, as a resident at New York University, that I heard Peter Medawar address issues of individuality (specificity) and cellular response in transplant rejection. Anyone who ever heard Medawar speak was struck not only by his eloquence of exposition but by the infectious enthusiasm that he brought to his subject. His talk was a major stimulus in determining my earliest studies in the field, in the laboratory of Kurt Hirschhorn at NYU, a story that I have recently reviewed (1).*

My first work attempted to create *in vitro* a system that might replicate some of the *in vivo* events that occur in graft rejection. This led to the description of the mixed leukocyte culture (MLC) test (2), in which we attempted to address both issues that Medawar had discussed: the specificity of the response, focusing on recognized antigens (1); and the cellular basis of the response, which I shall in large measure address here with regard to work from my own laboratory.

The basic response that is the assay of the MLC reaction concerns the proliferation of responding lymphocytes. [I previously discussed the development of a one-way method that allowed the selective study of a potential recipient's response to donor antigens (3)]. A major motivation was an attempt to recreate in MLC the lymphocyte response seen *in vivo*. What must be realized is that in 1963-1964, there was no recognition of different populations of lymphocytes; work in the late 1960s gave us the information that T and B cells are functionally disparate populations.

Our first MLC studies had little to do with study of the responding cells. After developing a one-way MLC stimulation system [initially using mitomycin C (3) and later x-irradiation (4)], we were interested in characterizing the genes that controlled the antigens that presumably stimulated response. Approximately 25 percent of MLCs between siblings did not result in detectable proliferative responses (5), allowing analyses [detailed elsewhere (1)] that showed: a) a single genetic system with 15 or more alleles controlled the antigen stimulating response in MLC (6); b) reactivity, or the lack thereof in MLC, predicted skin graft rejection times (7); c) the genetic system controlling reactivity in MLC was the same as that controlling the serologically-defined antigens being studied by Amos, Ceppellini, van Rood, Payne, Dausset, and others (8); d) the genetic system controlling reactivity in MLC was, in all likelihood, the major histocompatibility complex in humans (6); and e) the genetic region of the HLA complex stimulating the proliferative response in MLC was probably what we today call the HLA-D region (8,9), a finding later investigated elegantly by Yunis and Amos (10).

Simonsen raised a major issue, suggesting that T cells may be totipotent and, thus, do not show clonal distribution (11). As I then discussed with Morten Simonsen, the concept seemed to make analyses such as those that we were undertaking un-necessarily complex. Nonetheless, admittedly there was no formal proof that the response (as studied in MLC, for instance) was clonal. At that time, David Zoschke, a student in my laboratory, was searching for a thesis project and proceeded to test the hypothesis that T cells responding in MLC were totipotent. The protocols we devised were based on the idea that if we could stimulate cells with one allogeneic stimulus, eliminate those cells from the responding cell population, and subsequently show that the remaining cells were no longer responsive to the initial stimulus but did respond to a third-party stimulus (and vice-versa), we could then reject the Simonsen hypothesis. Dr. Marilyn Bach, my active colleague in research at that time, proposed that we incorporate *BUdR* into the MLC dividing cells and treat with light to eliminate those cells.

---

*I recently had the opportunity to write a similar chapter for the "History of HLA: Ten Recollections" (1), also edited by Paul Terasaki. Several of the stories that I would have included here were detailed there; thus, I shall attempt to avoid too much repetition and simply refer to that chapter when appropriate.

We began our experiments using antigens to which the donor of the cells was sensitized (such as PPD or tetanus) and showed that the cells responding to PPD, for instance, were different from those responding to tetanus, and vice-versa. Furthermore, we demonstrated specificity of response (12). Although the experiments were done in part to establish the conditions needed to evaluate alloantigen response, we found that the technical details of showing specificity in MLC-responding cells were formidable. We wound up using up to 200 stimulator cells per responding cell to eliminate the response to the initial stimulating cells. Despite these difficulties, we were able to show specificity of response (13). David Zoschke, after receiving both a Ph.D. (with me) and then an M.D., later became my colleague again as we were both, quite independently, recruited to the University of Minnesota.

Although I have reviewed the story below in some detail (1), I feel I must include the development of the CML test - the combined analysis of proliferation and cytotoxicity - that was so important in the early to mid-1970s. That same year, assays for generating cytotoxic T cells (Tc) in MLC and assessing their activity were developed by Hayry and Defendi (14) and Hodes and Svedmyr (15) in mice, and Susan Solliday (now Solliday-Rich) and I (16) in humans. The specificity of the Tc response was demonstrated when we showed reciprocal specificity on lymphoblastoid cell line targets with help from Hayry and Defendi in the ^{51}Cr assay.

While my goal had been to study the genetic control of response in humans, around 1970 I decided that most of the studies I was considering would be most effective with mice. The work of Snell, Stimpfling, Shreffler, Bailey, and so many others in establishing the inbred recombinant and mutant strains differing at the major histocompatibility complex in mice (H-2) greatly facilitated the design and testing of protocols for anyone like myself.

The first question we addressed concerned the genetic control of MLC proliferative response with regard to the antigens within the H-2 complex that stimulate response. Dutton, et al had already shown that H-2 was the primary MLC response stimulator in mice (17), as we had previously found in humans (6). Professor Hilliard Festenstein and his colleagues showed that the MLS system, of which he was the discoverer, could also stimulate a proliferative response (18) in mice which was not seen in humans. The H-2 complex, which was previously thought to have many different regions, had recently been "simplified" into the H-2K and H-2D regions on the one hand and the H-2I region on the other. The classical histocompatibility antigens were associated with K/D; no antigens controlling immune response had been associated with the H-2I region. Thus, we assumed that it was the K/D antigens that were of import; however, we found that it was actually disparity at the H-2I region that resulted in the strongest proliferative responses in MLC. The specificity of this proliferative response suggested that the H-2I region does encode antigens that preferentially (as compared with the K/D antigens) stimulated the proliferative response (19,20); Meo and Shreffler provided similar data in other strains (21). Michael Widmer, who did most of the above work, was first a technician and then a student in my laboratory. He went on to get a PhD with me and became an extremely productive immunologist.

This work, while terribly exciting to us, was quickly complemented and surpassed in terms of excitement. Dolores Schendel, also a PhD student in the laboratory at that time, and Barbara Alter, who has been involved in so many of the key experimental systems we have studied over the years, asked about the genetic control of Tc generation. We found that: a) no detectable cytotoxicity was generated to I region disparities alone, despite the strong proliferative response evoked; b) neither a detectable proliferative nor a cytotoxic response was generated against K/D disparities alone; but c) both a strong proliferative and cytotoxic response were generated when both the K/D and I region disparities were present on the stimulating cell. Furthermore, the cytotoxic response was aimed very preferentially at the K/D antigens (22-25).

I referred to the H-2I region as encoding the lymphocyte-defined (LD) antigens because of their ability to evoke a proliferative response in T cells, and the K/D antigens as the serologically-defined (SD) antigens because they had classically been defined serologically. Eventually, the nomenclature became class II antigens for LD and class I for SD. While our initial experiments showed no cytotoxic response directed toward the I region antigens, we later amended that finding to show that low-level cytotoxicity could be generated in some combinations (25). Nevertheless, we continued to champion the concept that the K/D antigens were functionally different from the I-region encoded antigens. This clearly offended some who said that this suggestion was based "merely" on quantitative differences. Eventually, even our most ardent opponents recognized those differences.

It amazed me then, as it does now, how much emotion can be evoked by terminology. It is still not clear to me whether the vehement reactions evoked by this concept (ie, that the class II antigens were functionally different from class I antigens) were related more to the actual concept or to the LD-SD terminology. Ultimately, the idea that class I and class II antigens differ not only from a structural but also from a functional point-of-view became a central tenet of immunology. Our early 1970s discovery came before any such observations were made in restricted response systems and was the experimental high point in our studies of the relationship of antigens encoded by the MHC and T-cell response.

Eisjvoogel had shown us very similar data in humans (26), as I recently discussed in detail (1). He did not, however, have an explanation for these findings. I suggested that his and our findings could be explained as follows (27): First, two functionally differing subpopulations of T cells were responding preferentially to the K/D and I regions, respectively. The very strong proliferative response seen was primarily that of helper T cells (Th) responding to I region antigens; the cytotoxic T cells (Tc) responded primarily to K/D antigens. Second, there was collaboration between these two populations of cells in that the I region-responsive proliferating cells provided help that allowed the functional maturation of the Tc. The schematic that accompanied the 1972 paper in which I first presented this idea is shown in Figure 1. This concept occupied us experimentally for the next two years; the model that evolved is shown in Figure 2.

Schendel and Alter did extensive studies of multiple strains (22-25), from which they developed what turned out to be a most useful system. Using the recom-

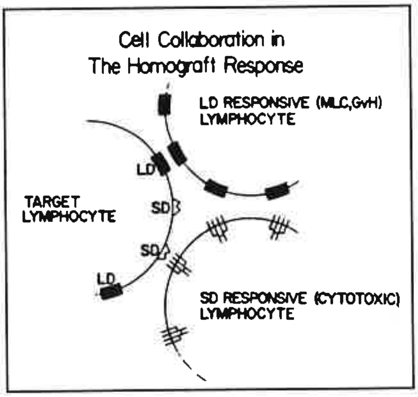


Figure 1. Helper T-cell and cytotoxic T-cell collaboration in the homograft response.

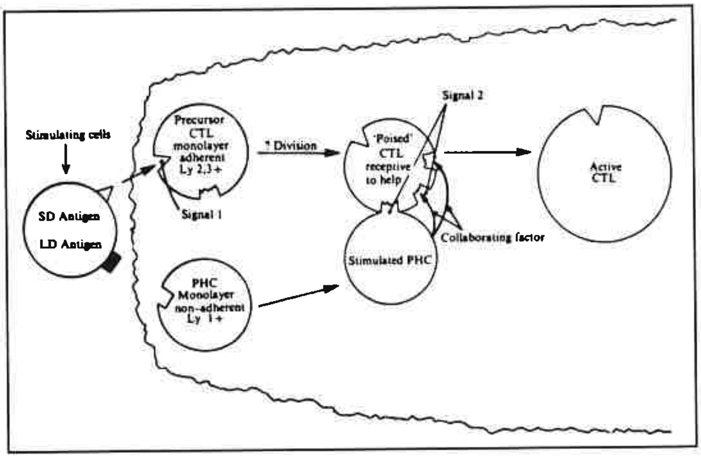
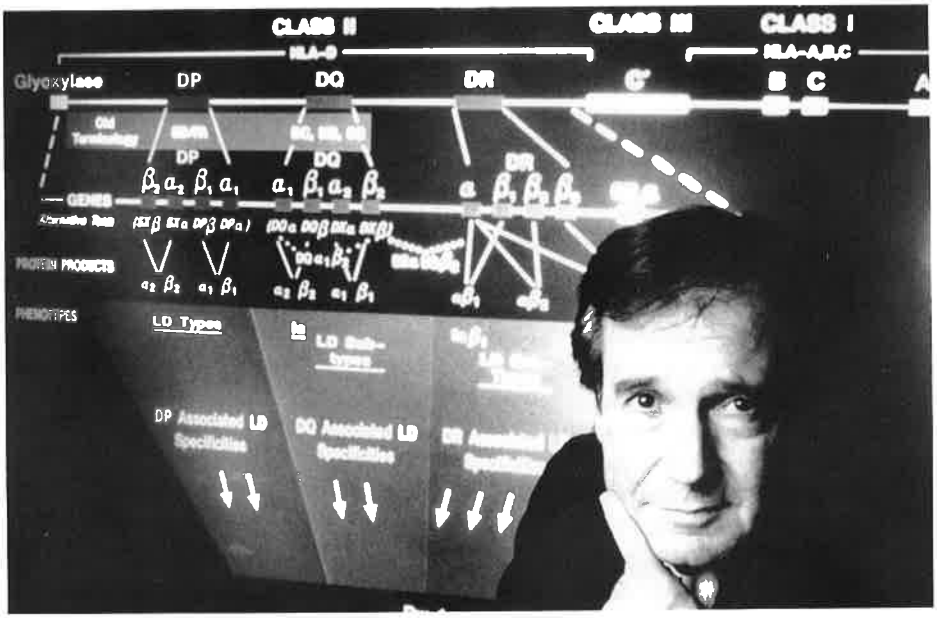


Figure 2. Helper T-cell and cytotoxic T-cell cooperation model.

Recent photo.



binant inbred strains, they stimulated the cells of a given responder strain with two sets of stimulating cells: one that differed from the responding cells only by class I antigens and the other that differed only by class II antigens. Thus, the responding cell population was confronted with one or both of the class I and class II antigens but on different cells (23). Using appropriate strain combinations, it was also possible to compare this separate presentation of class I and class II to having both antigens on one stimulating cell. Many questions that would have been impossible to study in a normal MLC could be probed by this system. I shall give some examples.

We were interested in the relative quantitative effect of presenting the antigens separately rather than on the same cell to determine whether and to what extent there may be linked recognition in the T-cell system as in antibody production. Our studies demonstrated that the three-cell approach, in which the class I and class II antigens are presented on separate cells, was only about 10 percent as effective at generating a cytotoxic response than presenting those same antigens on a single stimulating cell.

This system answered a different question that turned out to be of even greater interest. Dolores Schendel asked what effect the addition of class I and class II differences to the responding cells would have on generating a maximal cytotoxic response (25). She found that addition of the class I stimulus cells at time zero followed by the class II stimulus cells after 24 hours appeared optimal.

The following model was formulated through discussions with Paul Sondel, who had such an enormous creative influence on the laboratory for many years. We suggested that a class I stimulus alone was not sufficient to effect the full differentiation of Tc; however, that signal did lead the cytotoxic precursor cell to become responsive to help (to upregulate the IL2 receptor). We called this class I stimulus signal 1 to the precursor Tc, analogous to Bretscher's and Cohn's signal 1 in the B-cell system. The addition of the precursor Th signal 24 hours later then allowed the generation of help (IL2 and perhaps other lymphokines) as those precursor Th responded to class II antigens. We reasoned that by the time the Th were present to help, the differentiating Tc would be receptive to that help and be able to differentiate maximally thereafter, both in terms of proliferation and acquisition of the cytotoxic phenotype (28). This was the first suggestion that lymphocytes responded to antigens by becoming responsive to help, a model that has since been extensively supported and studied by many laboratories and was the basis for our "two-signal model" of Tc activation.

I must mention here the studies of Lafferty and colleagues (29,30). Kevin Lafferty and I have enjoyed a friendship that continues strongly today and has involved vehement arguments and - I think he would agree - competition at various times over many years. Kevin had his own two-signal model for the activation of T cells; much of the basis for our argument concerned the following. I emphasized that a functionally different T cell (Th) provided help to the maturing cytotoxic Tc. Kevin emphasized that the antigen-presenting cells provided a signal to the T cell. As is so often the case, I think we may have both been correct. Kevin was focusing on the functional maturation of Th and showed that the APC made some factor that facilitated the Th response. With regard to present models, it now appears that Kevin was concerned with IL1 and I with the IL2 produced primarily by Th. Incidentally, I think that it was the work of Barbara Alter and others in the laboratory (31,32) that provided the first evidence for what was in all likelihood IL1: a soluble factor that reconstituted the response of lymphocytes that had been depleted of APC (adherent cells). Since that time, of course, many laboratories have elucidated the steps and signals involved in the functional maturation of both T and B cells.

Karen Zier, another student in the laboratory, attempted to obtain support for the concept of Th responding to class II antigens as a separate population from the Tc responding to the class I antigens (33). As in other studies absorbing Tc to monolayers, we separated the Tc (monolayer adherent) from the Th, which were found in the culture supernatants. Combined with the immunogenetic studies and the three-cell experiments, we felt confident that the dichotomy of Th and Tc response to class II and class I antigens, respectively, and the collaboration between these two-cell types (that we had called an LD-SD collaboration) was a reasonable working model.

With Hans Sollinger (34) and later with Isakov (35), I attempted to test the extent to which there might be a collaborative response to class I and class II antigens *in vivo* and found some evidence for the phenomenon. Given the continuing controversy concerning the cellular basis for allograft rejection, I think these topics will continue to challenge us. I believe that Th, in their response to class II antigens (perhaps involved with endothelial cell activation), are of paramount importance for the rejection of many types of grafts (36-38). That Tc can be involved in rejection also seems established; others, as well as ourselves, demonstrated that cloned Tc can affect graft rejection (39). The mechanism remains in question, however, given the finding that Tc can produce lymphokines such as IL2, as reviewed immediately below.

Barbara Alter and I, with others in the laboratory, were intrigued by the finding that K/D (class I) antigens, without the presence of allogeneic class II antigens on the MLC stimulating cells, could lead to both a proliferative response and the generation of antigen-specific cytotoxicity. If help really was needed to allow the functional maturation of Tc, several alternatives would have to be considered to explain the generation of cytotoxicity directed toward the isolated class I disparities. Nancy Reinsmoen, Andreas Anichini, and I later showed the same was true for humans (40). While we considered several possibilities, including the response of Th to class I antigens, Barbara Alter suggested that perhaps there were helper-independent Tc because they produced their own IL2 (41). Shortly thereafter, Michael Widmer showed that such bifunctional Tc exist (a finding made at the clonal level) in mice (42), and Siew-Lin Wee made similar findings in humans (43). We referred to these cells as helper-independent Tc (HITc) in papers, and as "HIT" cells in more informal discussions. Extensive studies by Derry Roopenian, as part of his PhD thesis, showed that the amounts of IL2 produced by the Tc varied from undetectable to levels that, while very significant, were still much less than the IL2 produced by classical CD4+ (L3T4+) Th (44,45).

While I have already told the story recounted below (1), I will take the liberty of including it here because it is the most relevant to our work in transplantation and perhaps the only real example of my own direct involvement in clinical transplantation. In 1968, I had one of the most rewarding experiences of my career. I met Dr. Robert Good when he interviewed me for an Advanced Research Fellowship of the American Heart Association; all interviews should proceed similarly, from the applicant's perspective: Arriving at his office 20 minutes late, during which time I had the expected palpitations, Dr. Good entered with boundless energy, smiled broadly, and ushered me into his office; he took less than a minute to assure me that he thought my proposal was excellent, that I would get the fellowship I had applied for, and that he wanted me to relax so he could learn more about immunogenetics (the topic of my proposal). In fact, over the next 18 hours - our conversation lasted until 4 AM - Good guided me along the path that he had forged for the entire medical community. He considered immune deficiencies to be "experiments of nature" and felt that understanding children with immune deficiency diseases would lead us to an understanding of immunology. The remarkable visions of this truly brilliant clinical investigator led to a series of collaborative investigations that convinced many that I had worked with Bob; in fact, I never had.

Bob and I had interacted intensely on several occasions, including a workshop on immune deficiency disease at which bone marrow transplantation was discussed. During the following months, Hilaire Meuwissen, then working with Bob, visited my laboratory in Madison to learn the MLC method. As an assistant professor in Madison in 1968, I received a call from a pediatrician at Columbia Presbyterian Hospital in New York asking whether I would consider doing a bone marrow transplant on a 23-month-old boy with Wiskott-Aldrich syndrome. It turned out that the referring physician had initially called Bob Good, but Good had declined to accept the boy as a patient. Good referred him to me, telling him that perhaps I would consider the procedure. After some hasty reading, I agreed to attempt to match the patient, David Zeissett, with his sister. They were identical in MLC and we (including the invaluable assistance and support of Dr. Mortimer Bortin, who had until then done bone marrow transplants in mice) performed what became one of the first successful, matched bone marrow transplants (46).

The other transplant was done in Minneapolis by Good and colleagues (47). Their patient, with severe combined immunodeficiency disease, had a potential sibling donor. However, the patient was mismatched with the donor for one class I antigen. Bob was concerned about performing the transplant with the incompatibility and called me to discuss this situation. I suggested that MLC identity would be important to assess and we subsequently tested the blood of the patient and the potential donor in Madison (I believe they were also tested in Minneapolis by Hilaire Meuwissen) and found non-reactivity. The patient was then transplanted. Quite independently, Jon van Rood teamed with van Bekkum and DeVries to perform a transplant, also in a patient with severe combined immunodeficiency disease.

I must now, as I did in *History of HLA* (1) with all sincerity and gratitude, acknowledge my colleagues who contributed so much to the work that I have discussed here. The very productive careers that many of them have enjoyed since leaving my laboratory attests to their abilities and commitment to the field. For them and myself, the future in transplantation is truly very exciting. I, and several of my former colleagues, have recently begun to focus once again on the problems of discordant xenografting (perhaps pig to human). For myself, this line of investigation not only provides new challenges (eg, understanding and manipulating vascular endothelium) but also offers the opportunity to use the tools of molecular genetics, which have entranced us all, in a potential clinical setting.

Thus, while I was invited and have attempted to recount the past in this chapter, focusing on past work from my own laboratories, it is the future that seems so very exciting to all of us. Perhaps, as milestones continue to be reached and history continues to be written, another similar volume will soon be due.

REFERENCES

1. Bach FH. The T lymphocyte perspective of HLA: A personal reflection. In: Terasaki P, Ed. History of HLA: Ten Recollections. UCLA Tissue Typing Laboratory, Los Angeles, 1990; 189.
2. Bach FH, Hirschhorn K. Lymphocyte interaction: a potential histocompatibility test in vitro. Science 1964; 143:813.
3. Bach FH, Voynow NK. One-way stimulation in mixed leukocyte cultures. Science 1966; 153:545.
4. Bach FH, Bach ML. Comparison of mitomycin C and X-irradiation as blocking agents in one-way mixed leukocyte cultures. Nature New Biol 1972; 235:243.
5. Bach FH. Lymphocyte reactivity in mixed leukocyte cultures--its assay and genetics. In: Dawe CJ, Ed. In Vitro, II: Phenotypic Expression. Waverly Press, Baltimore, 1966; 32.
6. Bach FH, Amos DB. Hu-l: major histocompatibility locus in man. Science 1967; 156:1506.
7. Bach FH, Kisken WA. Predictive value of results of mixed leukocyte cultures for skin allograft survival in man. Transplantation 1967; 5:1046.
8. Amos DB, Bach FH. Phenotypic expressions of the major histocompatibility locus in man (HL-A): leukocyte antigens and mixed leukocyte culture reactivity. J Exp Med 1968; 128:623.
9. Bach FH, Albertini RJ, Amos DB, et al. Mixed leukocyte culture studies in families with known HL-A genotypes. Transplant Proc 1969; 1:339.
10. Yunis EG, Amos DB. Three closely linked genetic systems relevant to transplantation. Proc Nat Acad Sci 1971; 68:3031.
11. Simonsen M. Cold Spring Harbor Symp Quant Biol 1967; 32:517.
12. Zoschke DC, Bach FH. Specificity of antigen recognition by human lymphocytes in vitro. Science 1970; 170:1404.
13. Zoschke DC, Bach FH. Specificity of allogeneic cell recognition by human lymphocytes in vitro. Science 1971; 172:1350.
14. Hayry P, Defendi V. Mixed lymphocyte cultures produce effector cells: model in vitro for allograft rejection. Science 1970; 168:133.
15. Hodes RJ, Svedmyr EAF. Specific cytotoxicity of H-2 incompatible lymphocytes following mixed culture in vivo. Transplantation 1970; 9:470.
16. Solliday S, Bach FH. Cytotoxicity: specificity after in vitro sensitization. Science 1970; 170:1406.
17. Dutton RW. Spleen cell proliferation in response to homologous antigens studied in congenic resistant strains of mice. J Exp Med 1966; 123:665.
18. Festenstein H, Sachs JA, Abbasi K, et al. Serologically undetectable immune responses in transplantation. Transplant Proc 1972; 4:219.
19. Bach FH, Widmer MB, Bach ML, et al. Serologically defined and lymphocyte defined components of the major histocompatibility complex in the mouse. J Exp Med 1972; 136:1430.
20. Bach FH, Widmer MB, Segall M, et al. Genetic and immunological complexity of major histocompatibility regions. Science 1972; 176:1024.
21. Meo T, Vives J, Miggiano V, et al. A major role for the Ir-1 region of the mouse H-2 complex in the mixed leukocyte reaction. Transplant Proc 1973; 5:377.
22. Alter BJ, Schendel DJ, Bach ML, et al. Cell-mediated lympholysis: importance of serologically defined H-2 regions. J Exp Med 1973; 137:1303.
23. Schendel DJ, Bach FH. Genetic control of cell-mediated lympholysis in mouse. J Exp Med 1974; 140:1534.
24. Alter BJ, Bach FH. Role of H-2 lymphocyte-defined and serologically-defined com-

ponents in the generation of cytotoxic lymphocytes. J Exp Med 1974; 140:1410.

25. Schendel DJ, Bach FH. H-2 and non-H-2 determinants in the genetic control of cell-mediated lympholysis. Eur J Immunol 1975; 5:880.

26. Eisjvoogel VP, duBois MJGJ, Meinesz A, et al. The specificity and activation mechanism of cell-mediated lympholysis (CML) in man. Transplant Proc 1973; 5:1675.

27. Bach FH. The major histocompatibility complex in transplantation immunology. Transplant Proc 1973; 5:23.

28. Bach FH, Bach ML, Sondel PM. Differential function of major histocompatibility complex antigens in T lymphocyte activation. Nature 1976; 259:273.

29. Lafferty KJ, Cooley MA, Woolnough J, et al. Science 1975; 188:259.

30. Lafferty KJ, Misko I, Cooley MA. Nature 1974; 249:275.

31. Bach FH, Alter BJ, Solliday S, et al. Lymphocyte reactivity in vitro. II. Soluble reconstituting factor permitting response of purified lymphocytes. Cell Immunol 1970; 1:219.

32. Alter BJ, Bach FH. Lymphocyte reactivity *in vitro*. I. Cellular reconstitution of purified lymphocytes. Cellular Immunology 1970; 1:207.

33. Zier KS, Bach FH. Secondary responses of human lymphocytes to alloantigens in vitro. Scand J Immunol 1975; 4:607.

34. Sollinger HW, Bach FH. Collaboration between *in vivo* responses to LD and SD antigens of the major histocompatibility complex. Nature 1976; 259:487.

35. Isakov N, Bach FH. Participation of class II alloantigens in vivo regulation of K/D region disparate thyroid graft rejection in mice. J Immunol 1985; 134:3480.

36. Bach FH. Reconsideration of the mechanism of first-set vascularized allograft rejection: some concluding remarks. Hum Immunol 1990; 28:263.

37. Bach FH. The cellular basis of graft rejection. Transplant Proc 1988; 20:353.

38. Bach FH. Transplantation immunobiology. In: Cinadar B, Miller RG, Eds. Progress in Immunology VI. Academic Press, New York, 1986; 976.

39. Biel LW, Morrow CE, Zhu XY, et al. Ability of donor sensitized bulk or cloned T lymphocytes to induce rejection of established pancreatic islet allografts. Transplant Proc 1985; 17(1):826.

40. Reinsmoen N, Anichini A, Bach FH. Clonal analysis of T lymphocyte response to an isolated class I disparity. Hum Immunol 1983; 8:195.

41. Alter BJ, Katz SA, Bach FH. Cellular basis of response to K-region class I MHC disparities. Transplant Proc 1983; 5(1):171.

42. Widmer MB, Bach FH. Antigen-driven helper cell-independent cloned cytolytic T lymphocytes. Nature 1981; 294:750.

43. Wee, Chen, Strassmann, et al. Helper cell independent cytotoxic clones in man. J Exp Med 1982; 156:1854.

44. Roopenian DC, Widmer MB, Orosz CG, et al. Responses against single minor histocompatibility antigens: I. Functional and immunogenetic analysis of cloned cytolytic T cells. J Immunol 1983; 131:2135.

45. Roopenian DC, Orosz CG, Bach FH. Responses against single minor histocompatibility antigens. II. Analysis of cloned helper T cells. J Immunol 1984; 132:1080.

46. Bach FH, Albertini RJ, Joo P, et al. Bone marrow transplantation in a patient with the Wiskott-Aldrich Syndrome. Lancet 1968; 2:1364.

47. Gatti RA, Meuwissen HJ, Allen HD, et al. Bone marrow transplantation of sex-linked lymphogenic immunological deficiency. Lancet 1968; 2:1366.

CURRICULUM VITAE

Fritz H. Bach

PERSONAL

Born:	April 5, 1934; Vienna, Austria
Children:	David, Peter, Wendy, Kathryn, Erika
Home Address:	34 Park Lane Minneapolis, MN 55416
Office Address:	Immunobiology Research Center Box 724 Mayo Memorial Bldg. University of Minnesota Minneapolis, Minnesota 55455

EDUCATION

1951-55	Harvard University, Cambridge, Massachusetts, A.B.
1956-58	Washington University School of Medicine, St. Louis, Missouri
1958-60	Harvard Medical School, M.D.
1960-63	Internship, First and Second year medical residency, Third and Fourth (New York University) Medical Division, Bellevue Hospital New York, New York

POSITIONS

1955-56	Research Associate, Beth Israel Hospital, Boston, Massachusetts
1963-64	Genetics Traineeship (USPHS), New York University Medical School, New York, New York
1964-67	Advanced Research Fellowship, American Heart Association
1967-73	Established Investigatorship, American Heart Association
1965-66	Instructor in Medicine, University of Wisconsin, Madison
1966-69	Assistant Professor, Departments of Medical Genetics and Medicine, University of Wisconsin, Madison
1969-72	Associate Professor, Departments of Medical Genetics and Medicine, University of Wisconsin, Madison
1972-73	Associate Professor, Departments of Medical Genetics and Surgery, University of Wisconsin, Madison
1973-80	Professor, Departments of Medical Genetics and Surgery University of Wisconsin, Madison
1974-79	Director, Immunobiology Research Center University of Wisconsin, Madison
1979-	Professor, Departments of Laboratory Medicine/Pathology and Surgery, University of Minnesota, Minneapolis

1979-	Director, Immunobiology Research Center University of Minnesota, Minneapolis
1987-90	Harry Kay Chair in Immunobiology, University of Minnesota, Minneapolis
1990-	Helen and Milton Kimmelman Chair in Fundamental Immunobiology

PROFESSIONAL SOCIETIES

American Society for Clinical Investigation
American Association of Immunologists
Transplantation Society

AWARDS

	Established Investigator of the American Heart Association
	Sumner Memorial Lecturer
1974	Modern Medicine, Distinguished Achievement Award
1977	Milwaukee Academy of Medicine, Distinguished Achievement Award
1979-84	Leukemia Society of America, National Board of Trustees
1983	American Red Cross, Distinguished Scientist Award
1984	Medal of the College de France
1985	Weizmann Institute, International Board of Governors
1987	Foreign Member, Royal Dutch Academy of Sciences
1989	The Emilio Trabucchi Foundation Award
1989	Charter Member, International Bone Marrow Transplant Registry

EDITORIAL BOARDS AND EDITORSHIPS

Proceedings of the Transplantation Society
Transplantation
Tissue Antigens
Journal of Immunology
Journal of Clinical Immunology and Immunopathology
Annales d'Immunologie
Human Immunology
Immunogenetics
Immunopharmacology
Immunology Today
Journal of Molecular Biology and Medicine
Editor, Clinical Immunobiology (with Dr. Robert A. Good)

COUNCIL AND ADVISORY COMMITTEE MEMBERSHIPS

Council Member, International Transplantation Society

Midwest Immunology Society

International Bone Marrow Transplant Advisory Committee

1977-78	Vice-Chairman
1978-80	Chairman

National Foundation, March of Dimes, Clinical Research Committee

National Cancer Institute, Immunolgoy Contract Committee

International Histocompatibility Testing Workshops, Councillor

National Institutes of Health, Experimental Immunology Study Section

Medical Science Review Committee, Juvenile Diabetes Foundation

PUBLICATIONS

Total: 549

REFLECTIONS OF A XENOTRANSPLANTER

Keith Reemtsma

Address: Department of Surgery
Columbia-Presbyterian Medical Center
622 West 168th Street
New York, New York 10032

Keith Reemtsma

REFLECTIONS OF A XENOTRANSPLANTER

Keith Reemtsma

In the fall of 1963, I began transplanting kidneys from nonhuman primates into patients. The work was highly controversial, and the results were, to many, surprising.

At the time of these studies, over a quarter century ago, we had the immunosuppressive drugs azathioprine and steroids, but we did not have chronic dialysis or cadaveric grafting. Patients who did not have a family donor had no treatment. Under these circumstances, we believed it was ethically appropriate to explore the use of nonhuman donors.

On the morning of November 5, 1963, I went to the operating rooms of Charity Hospital in New Orleans to exchange a few words with my patient, a 43-year-old dock worker in kidney failure. I had spent a long time with him over the past several weeks explaining what I planned to do, and he had agreed.

Then I went to Tulane Medical School, next door to Charity Hospital, and shaved a chimpanzee that had been discarded, because of irascibility, by a circus. He had been selected as a donor based on body size and blood group.

Then I took the chimpanzee on a journey to Charity Hospital. We had two operating rooms, one for the donor and one for the recipient. I started with the donor, then went into the recipient room. I was implanting the kidneys in the recipient when my boss, Oscar Creech, walked into the room. "Nice job," he said, "looks fine."

My first assistant, a resident on the Tulane Surgical Service at Charity Hospital, was not as kind as my boss. He often kidded me about my background. "Keith," he said, "if this doesn't work you can always go back to the Navajo Reservation and straighten out the hymnals and pass the collection plate."

Drs. Keith Reemtsma (left) and Charles Dubost at the Godrey Nuose Dinner in honor of Dr. Charles Dubost in October 1972 at the Wine Room, Pierre's.

The operation worked (Fig. 1). Urine began flowing immediately, and within three days his BUN and creatinine clearance were normal. A rejection response on the fourth postoperative day was reversed, and he was discharged after seven weeks with normal renal function. Two weeks later he was hospitalized with pneumonia. He died of infection, and autopsy showed normal kidneys.

The next month I did another patient, who survived for nine months. The courses of these patients are summarized below:

CASE REPORTS:

All patients were in terminal uremia necessitating dialysis and all patients received pretransplantation treatment of aza-thioprine, actinomycin C, and steroids. Selection of the donor was based on body size and blood typing of donor and recipient. In each instance the donor received general endotracheal anesthesia, with monitoring of blood pressure, electrocardiogram and body temperature. Creatinine clearance was determined in each donor. At moderate hypothermia (about 30°C) the entire renal complex, including both kidneys and ureters, aorta, and vena cava, was removed en bloc after anticoagulation and was irrigated (Fig. 2).

Patients were prepared simultaneously by extraperitoneal exposure of the external iliac artery and vein. In each instance the aorta and vena cava of the graft were anastomosed to the recipient's external iliac artery and vein, respectively, in an end-to-side fashion (Fig. 3).

The periods of ischemia, from the time of vessel clamping in the donor until blood flow was restored through the graft in the recipient, varied from 36 to 43 minutes. All patients received postoperative azathioprine, actinomycin C, steroids, and x-irradiation to the transplant.

Case 1

This 43-year-old former dock worker with a history of hypertension since 1957, was admitted to the Veterans Administration Hospital, New Orleans, in 1959.

Renal biopsies showed nephrosclerosis and chronic glomerulonephritis. He was treated with dietary management, including salt restriction. He was readmitted in June 1963, because of progressive uremia, hypertension, and congestive heart failure. Laboratory studies included the following: BUN, 240 mg%; creatinine, 14 mg%; and creatinine clearance 8 ml/minute. There was no improvement with dietary management, and peritoneal dialysis was required.

On November 5, 1963, he received a renal heterograft. During the first 14 hours post-transplantation, the urinary output was 6700 cc. The BUN which was 112 mg% on the day of operation, decreased to 39 mg% by the fourth day following transplantation. The creatinine which was 11.2 mg% on the day of operation fell to 1.5 mg% 48 hours posttransplantation. Four days after transplantation threatened rejection occurred but was reversed following local irradiation to the graft and increased doses of immunosuppressive drugs. His early course had been reported previously in detail. Function of the graft was confirmed by renograms, scans, and intravenous urogram.

On December 18th he was allowed to leave the hospital because he was asymptomatic and had normal renal function. He was readmitted on December 20th with a temperature of 39.4°C and radiographic evidence of an infiltrate in the right middle lobe with pleural effusion. Culture of the sputum revealed *Aerobacter aerogenes*. The dosage of azathioprine was lowered because of leukopenia, but

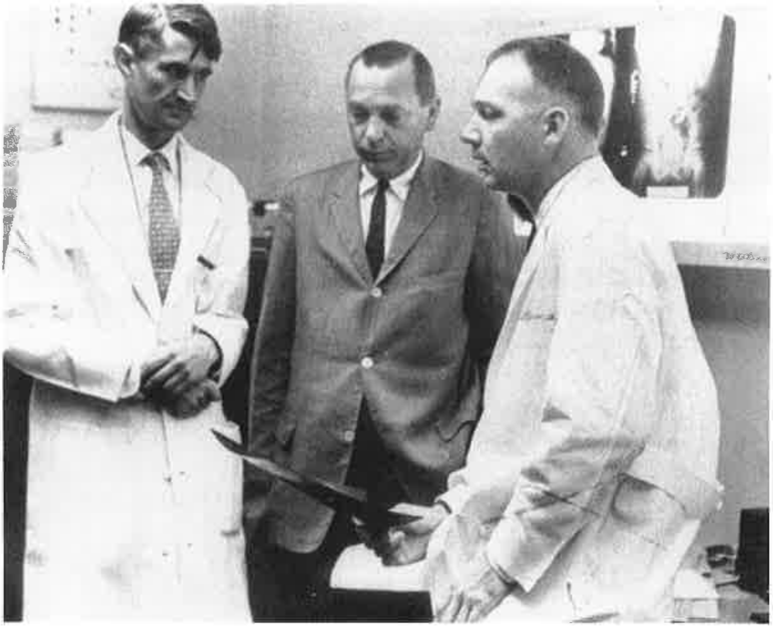


Figure 1. Members of the Tulane transplantation team: (left to right) Drs. McCracken, Schlegel, Reemtsma.

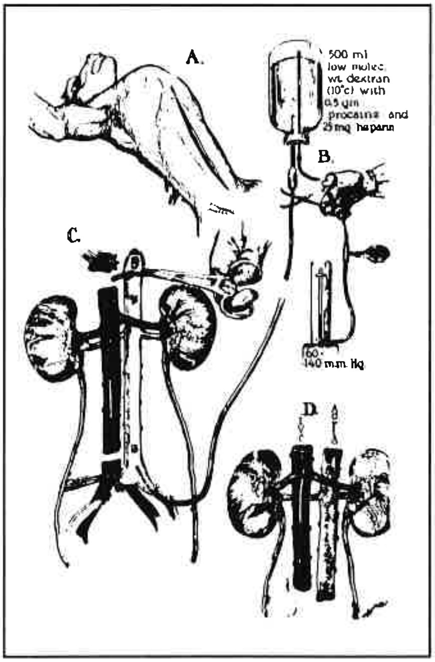


Figure 2. Donor operation with en bloc excision.

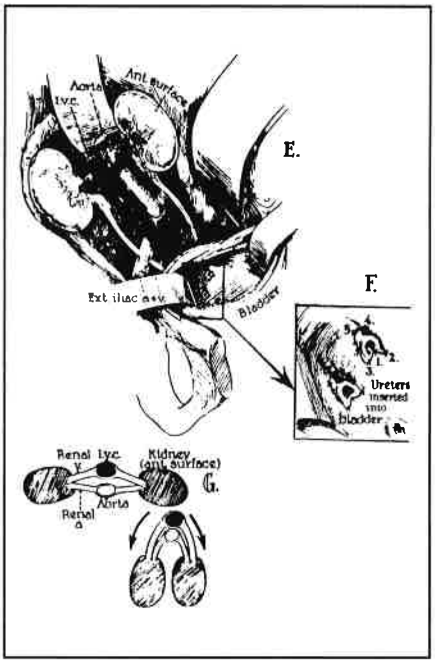


Figure 3. Implantation of xenografted kidneys into patient.

renal function continued satisfactorily. The patient's condition later deteriorated rapidly and he died 63 days after transplantation, following a period of shock apparently due to sepsis.

Autopsy showed acute bronchopneumonia, right lower lobe; acute tracheobronchitis; resolving abscess, right middle lobe. Transplanted kidneys showed acute tubular necrosis, consistent with shock; there was no cellular infiltrate or changes in the blood vessels (Fig. 4).

Case 2

This 23-year-old school teacher was admitted in November 1963 with chronic glomerulonephritis and progressive uremia. She had an episode of acute glomerulonephritis at 14 and persisting proteinuria. She had remained asymptomatic until approximately five months before admission when she noted weakness and dizziness. On admission her blood pressure was 190/120 and laboratory studies included BUN of 184 mg%, creatinine of 40 mg% and creatinine clearance of 4 ml/minute. Rapid deterioration of her condition necessitated peritoneal dialysis.

On January 13, 1964, she received a renal heterotransplant. Diuresis occurred with a urinary output on the day of operation of 7000 ml. By the third day following transplantation the BUN had fallen from a pre-transplant level of 116 mg% to 12 mg%, and the serum creatinine fell from a preoperative level of 21 mg% to 0.9 mg%. Creatinine clearance was 50 cc per min. Her blood pressure fell to normotensive levels, 110/70. Her subsequent course demonstrated satisfactory renal function until the 23rd day following operation when threatened rejection was suspected. Urinary output decreased to 1000 ml/24 hours, and BUN and creatinine rose to 28 and 1.9 mg%, respectively. Creatinine clearance fell to 31 ml/minute and urinary sodium content to 11.6 mEq for a 24-hour period. Gradual reversal of rejection occurred during the following two weeks, although unexplained fever persisted for three months. She was asymptomatic and had normal renal function 6.5 months after transplantation.

Serial renograms in this patient demonstrated a delay in peak activity which coincided with clinical and biochemical evidence of threatened rejection. Following reversal of rejection, the renogram resumed a more normal pattern. Intravenous urogram 12 weeks after transplantation showed function of both transplanted kidneys.

Agglutination studies in this patient demonstrated a slight rise in titer at approximately three weeks after transplantation. The agglutination titer subsequently returned to previous levels.

Nine months after transplantation, this patient died after a 24-hour illness of undetermined etiology. At autopsy all anastomoses were well-healed and the transplanted kidneys were grossly normal. Microscopic sections showed sub-intimal proliferation of medium-sized vessels (Figs. 5-7).

The original paper (1) included the following statements in the discussion.

"Our tentative and preliminary over-all findings suggested that the heterografted kidney from chimpanzee to man responded similarly to the homografted kidney from man to man. In an instance of renal homografting between sisters done the same week as the first heterograft, threatened rejection occurred four days after transplantation, following a similar pattern to that seen in Case 1 reported here. There is similarity in time and degree of clinical and chemical changes seen in these two patients, in the initial response to transplantation, in the period of threatened rejection, and in reversal of rejection (Fig. 8).

"Our further efforts will be directed toward defining the determinants of com-

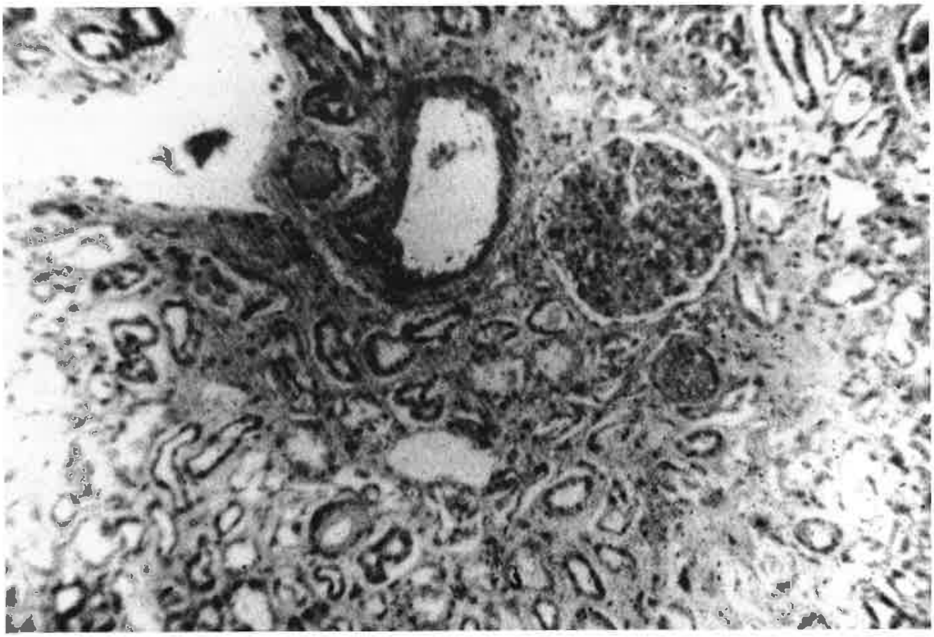


Figure 4. Histology of renal xenograft in Case 1.

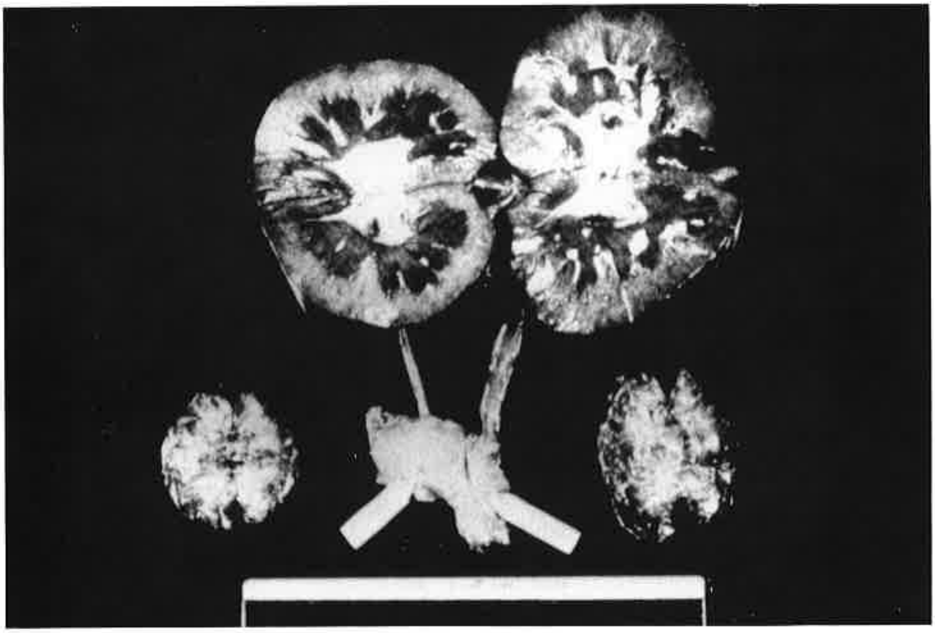


Figure 5. Gross specimens removed from patient who survived nine months with renal xenografts.

patibility in matching of donor and recipient; toward adjusting of immunosuppressive measure to permit acceptance of renal heterografts; and toward studies of the long-term function of such grafts in man.

"We would emphasize, however, that we regard this work as wholly experimental. Under these circumstances only the most stringent precautions will make such work justified and justifiable, and historic experience shows that the field of heterotransplantation may be abused flagrantly. The use of non-human kidneys in man removes the problems of the human donor, but the consequence of this exchange is increased difficulty imposed by cross-species transplantation. Whether heterografted kidneys will function often enough, well enough and long enough to warrant their continued use remains unanswered, but the present study suggests to us that further work in this area is indicated."

By 1965 chronic dialysis and cadaveric transplantation had become available, and we discontinued our clinical work in cross-species transplantation. However, I have continued laboratory work in xenografts for 25 years. Our most recent xenograft studies have involved cardiac transplants in primates and islet cell transplants in experimental and spontaneous diabetes.

The initial work in New Orleans confirmed our basic premise that non-human organs transplanted into humans could function similarly to human-to-human transplants. Our work now is directed toward an understanding of the fundamental nature of the xenograft reaction. The evidence is suggestive, but certainly not conclusive, that these processes may be modified sufficiently to permit, in the future, the use of non-human organs, tissues and cells in man.

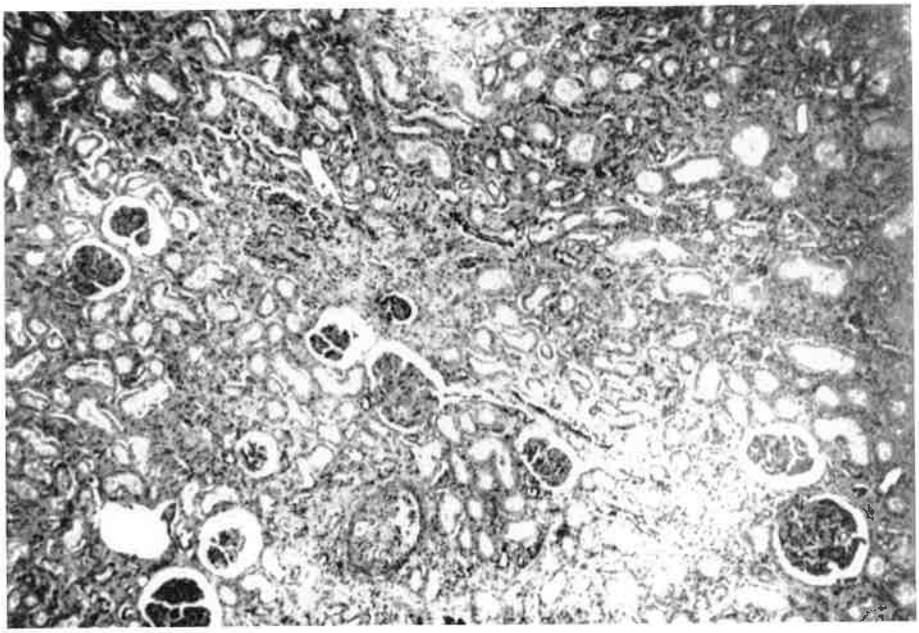


Figure 6. Histology of xenografted kidney in patient who survived nine months after transplantation.

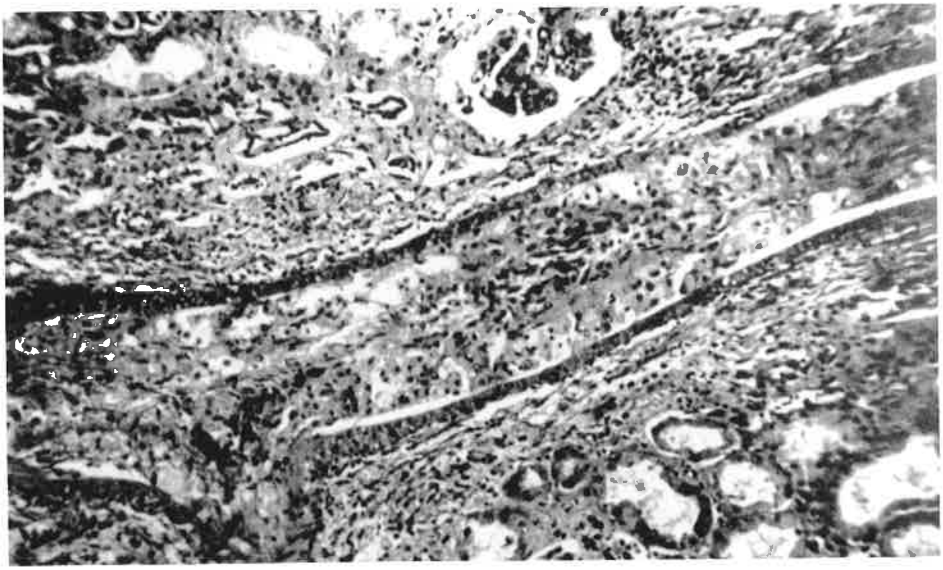


Figure 7. Histology of xenografted kidney in patient who survived nine months after transplantation.

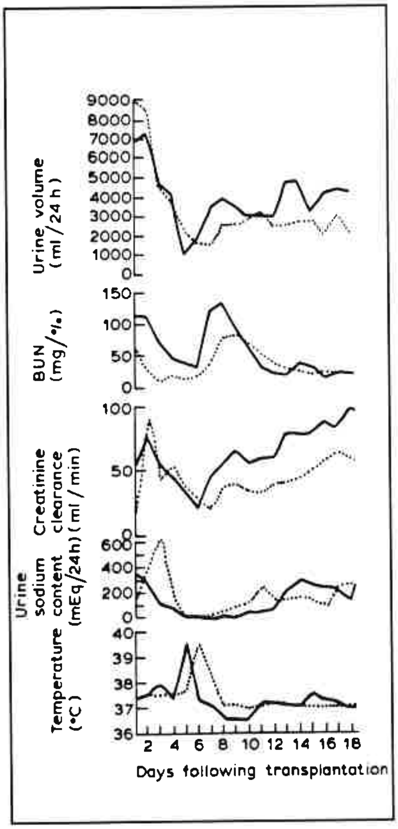


Figure 8. Courses of two patients, one following a sister-to-sister hemograft (dotted line), the other following a primate-to-man xenograft (heterograft) (solid line). Note similarity in courses, including appearance and subsequent reversal of rejection.

CURRICULUM VITAE

Keith Reemtsma

PERSONAL

Born: December 5, 1925; Madera, California

Home Address: 211 Central Park West
New York, New York 10024

Office Address: Department of Surgery
Columbia-Presbyterian Medical Center
622 West 168th Street
New York, New York 10032-3784

EDUCATION

	Primary, Public Schools of El Reno, Anadarko; McAlester, Oklahoma, and Fort Defiance, Arizona
1943	Secondary, Wasatch Academy, Mt. Pleasant, Utah
	Idaho State University, Pocatello, Idaho, B.S.
1949	University of Pennsylvania, M.D.
1958	Columbia University, Medicine Sc.D.

BOARD CERTIFICATION

1954	National Board of Medical Examiners
1958	American Board of Surgery
1960	Board of Thoracic Surgery

LICENSURE

California
Louisiana
New Mexico
New York
Utah

MILITARY SERVICE

1951-53	Lieutenant, MC, USNR, U.S. Naval Hospital, Philadelphia, Pennsylvania; Field Medical Service School, U.S. Marine Corps, Camp LeJeaune, North Carolina; U.S. Navy Surgical Team 16, Far East Command (USN Hospital Ship Repose, Inchon, Korea; 3rd and 14th Army Field Hospital, Pusan, Korea; "E" Company, First Medical Battalion, First Marine Division FMF (Korea); U.S.N.H. Yokosuka, Japan)
1953	Released from Active Duty
1955	Honorable Discharge

POSITIONS

1950-51	Intern, The Presbyterian Hospital, New York
1951/1954-55	Assistant Resident in Surgery, The Presbyterian Hospital, New York
1956	Resident in Surgery, The Presbyterian Hospital, New York
1957	Chief Resident in Surgery, The Presbyterian Hospital, New York
1957	Assistant in Surgery, Columbia University College of Physicians and Surgeons, New York
1957-62	Assistant Professor of Surgery, Tulane University School of Medicine
1962-66	Associate Professor of Surgery, Tulane University School of Medicine
1966	Professor of Surgery, Tulane University School of Medicine
1966-71	Professor and Head, Department of Surgery, University of Utah College of Medicine
1966-71	Director, Surgical Service, University of Utah
1971-	Director, Surgical Service, The Presbyterian Hospital
1971-	Professor and Chairman, Department of Surgery, Columbia University College of Physicians and Surgeons

PROFESSIONAL SOCIETIES

- Alpha Omega Alpha
- American Association for Thoracic Surgery
  - 1991 President
- American Board of Surgery
- American College of Surgeons
- American Federation for Clinical Research
- American Medical Association
- American Surgical Association
- International Cardiovascular Society
- Halstead Society
- National Institutes of Health
  - 1963-68 Surgery Study Section A
  - 1969-72 Graduate Education in Surgery (NIGMS)
- New York County Medical Society
- New York Society for Thoracic Surgeons
- Salt Lake County Medical Society
- Salt Lake Surgical Society
- Society of Clinical Surgery
  - 1969-73 Membership Committee
  - 1979 Chairman, Membership Committee
  - 1976 President
- Society of University Surgeons
  - 1962-75 Treasurer

Society for Vascular Surgery
Southern Society for Clinical Research
Southern Thoracic Surgical Association
Surgical Biology Club II
Western Surgical Association

COUNCIL AND ADVISORY COMMITTEE MEMBERSHIPS

1965-70	Advisory Council on Thoracic Surgery, American College of Surgeons
1968-72	Program Committee, American College of Surgeons
1967-74	International Relations Committee, American College of Surgeons
1968-70	Planning Committee, American Board of Surgery
1970	Nominating Committee, American Board of Surgery
1971	Committee on Certification for Special Competence, American Board of Surgery
1971-74	Committee on Graduate Education, American College of Surgeons
1968-74	Advisory Membership Committee, American Surgical Association

PUBLICATIONS

Total: 35 Book Chapters
300 Journal Publications

THE FIRST HUMAN-TO-HUMAN HEART TRANSPLANT

Christiaan N. Barnard

Address: P.O. Box 6143
Welgemoed 7538
71 Kommisaris Street
Welgemoed 7530
South Africa

1967

C. N. Barnard

1990

THE FIRST HUMAN-TO-HUMAN HEART TRANSPLANT

C. N. Barnard

Prolonged surgical procedures on the human heart, without the danger of anoxic damage to other vital organs, became possible only after a technique was developed whereby the venous return could be diverted to an extra-corporeal system for oxygenation and returned to the arterial tree. This allowed the heart and lungs to be excluded from the circulation with adequate perfusion of the rest of the body with oxygenated blood.

Further progress in cardiac surgery depended mainly on the introduction of new surgical techniques and the detection and management of the problems inherent in these new procedures.

From the outset, we did not consider the transplantation of the human heart as a scientific breakthrough, but merely as the introduction of a new technique in the treatment of heart disease and were, therefore, surprised by and ill-prepared for the publicity and controversy that followed this operation.

There are several steps to be taken before a new surgical procedure can safely be attempted in the operating room.

First, the surgical team should, as far as possible, explore the technical difficulties to determine that the procedure can be performed with an acceptable risk to the patient. Secondly, the problems inherent in the new procedures must be identified as thoroughly as possible and methods to cope therewith must be developed. Both these steps often require the use of human cadavers in the postmortem room, live animals in the laboratory, and the published experiences of researchers in the same field. We made sure that we were well prepared in both respects before performing the first human-to-human heart transplant on December 3, 1967.

The Surgical Technique

Experimental orthotopic transplantation, whether autotransplantation or homotransplantation, without supportive techniques were universally unsuccessful in obtaining survivors for longer than a few hours (1).

Only with the advent of methods of supporting the circulation during the operative procedures could surgical techniques for excising the recipient's heart, then replacing it, either as an auto- or homotransplant, be developed.

Anastomosis of the aorta and pulmonary arteries presented little problem, but reestablishing the systemic and pulmonary returns were technically difficult until 1959 when Cass and Brock (2) suggested that portions of the patient's left and right atria should be left and these anastomosed to the corresponding atria of the donor's heart.

Using this technique, one year later Lower and Shumway (3) reported the first consistently successful results in animal experiments.

Armed with these results and those of other researchers in the same field, in 1965 we started a research program in the animal laboratory, focusing on the problems of both renal and heart transplants.

In the following three years, numerous canine cardiac allografts were performed until we were satisfied that the surgical team could perform a heart transplant with minimal risk.

We do not claim to have made any contribution to the surgical technique of orthotopic transplantation of the heart except to modify the operation after the first human transplant to ensure that the S.A. node of the donor heart would not be damaged during excision (4).

Associated Problems

In identifying the problems that would be encountered after cardiac transplantation, we had the advantage of drawing on the experiences of surgical teams which were already involved in kidney and liver transplantation. It appeared that these main concerns would be patient selection, donor availability, the diagnosis and treatment of rejection, and the complications of immunosuppression. In many ways these problems in a cardiac transplant program would be similar to those experienced in the transplantation of other organs. For that reason we decided to get both laboratory and later clinical experience in kidney transplantation.

During early 1967, I decided to gain some clinical experience with human kidney transplantation and therefore spent three months with the late Dr. David Hume at the Medical College of Virginia where Dr. Richard Lower was working in the field of cardiac transplantation. It was during this visit that I was accused of stealing the idea of cardiac transplantation from Dr. Lower. If this were the case, I must have been the best student he ever had for I never worked with him and only visited his laboratory once for 30 minutes while he was doing a heart transplant on a dog.

After leaving Richmond, I went to Denver to visit Dr. Starzl, mainly to learn about his work on antilymphocyte serum.

On my return to Cape Town we decided to start a kidney transplant program first, as an introduction to heart transplantation. This would give us the opportunity to organize a transplant team and introduce us to the practical problems of human organ donation in South Africa and the complications encountered with the use of immunosuppressive drugs.

In September 1967 we performed a kidney transplant on Mrs. Black. The kidney was donated by an African male. In those days South Africa was still very color conscious, and I was not surprised to read the newspaper headlines the next day: "Mrs. Black gets black kidney." The patient survived 20 years with that kidney. I assume that I have the best results with kidney transplantation in the world, as this was the only kidney transplant I ever performed and therefore have achieved a 100% 20-year survival!!

After this kidney transplant, we considered that the team was ready to embark on a human heart transplant. The surgical technique had been rehearsed daily for three years in the animal laboratory by surgeons who had done over a thousand open heart procedures since mid-1958.

We had also performed a successful kidney transplant from a human donor and had successfully managed the problems associated with human donation and immunosuppression, and the precautions we took prevented any major complications in the immunosuppressed patient. The same team, facilities, and precautions would be used for the heart transplant, and the only decision that remained was the selection of a candidate for this operation.

Patient Selection

Several cardiac surgeons with whom I spoke at the time were of the opinion that they would only consider a cardiac transplant in a patient who had undergone open-heart surgery and who afterwards could not maintain adequate circulation without the support of the heart-lung machine. Provided that a suitable human donor was available in hospital at the time, they considered a heart transplant to be justified. I am of the opinion that this approach was mainly due to fear of litigation if the operation were unsuccessful.

As it was impossible to predict beforehand which patient would fail to survive after open heart surgery without circulatory support from the heart-lung machine, and as it was even more unlikely that a suitable human donor would be available at that stage, we decided on a different approach.

After extensive discussions with the late Professor V. Schrire, who as the head of the Department of Cardiology selected patients for all open-heart procedures, we concluded that a patient with intractable heart failure and impending death would be eligible.

The criteria for selection would thus be a patient who: a) suffered from extensive irreversible disease of the heart muscle; b) was uncontrolled by intensive medical treatment in hospital; and c) was not amenable to any previously practiced surgical procedure.

It should be pointed out that at this stage we did not recognize any contraindications and thought that a patient could not be too ill or too old to benefit from the improvement in circulation provided by the transplanted heart.

Looking back now, we recognize that this was a mistake and was the reason for many of the failures in the early days of cardiac transplantation. It was not that patients did not benefit from their new hearts, but the terminally ill patient, especially associated with certain complications, did not do well on the high doses of steroids that were used before the introduction of cyclosporine.

The first patient selected was a White 53-year-old male by the name of Louis Washkansky (5). In 1955 he was found to have diabetes. In 1959, 1960, and 1965 documented episodes of infarction occurred. Following the last attack, symptoms of myocardial insufficiency developed and progressed steadily despite intensive cardiac treatment which included digitalis, diuretics, aminophylline, and long-term anticoagulant therapy. His diabetic state was kept under control with oral agents. Because of progressive effort dyspnea, paroxysmal dyspnea, and congestive failure, he was admitted to the cardiac unit for assessment and special study in February 1967.

On examination he had all the features of severe right and left heart failure due to extensive ischemic destruction of the left ventricular muscle, confirmed by cardiac catheterization on February 14, 1967 (Table 1). The patient continued to work until August 1967 when he developed intractable failure which did not respond to medical therapy. At this stage it was apparent that further therapy would be ineffective. The patient was bedridden and totally incapacitated, with inadequate perfusion of all body tissues. After discussing the problems of heart transplantation, the patient accepted the risks of the procedure without hesitation.

Table 1.

Pressures		Blood Samples	
		% Saturation	Content (ml/l)
Right atrium	a=17		
	x=6 mean 10		
	v=10		
	y=8.5		
Right ventricle 85/15-19			
Pulmonary artery 75/38 mean 54		58.0	117.0
Right brachial artery 130/75 mean 90		96.5	198.0
Pulmonary capillary	a=40		
	x=32 mean 35		
	v=36		
	y=29		
Left ventricle 125/25-30			
Body surface area 0.95 sq m; hemoglobin=15.3 G/100ml; O_2 Capacity=205 ml/l; O_2 uptake=192 ml/min; cardiac output=2.36 l/min; cardiac index=2.43 l min/sq m; systemic vascular resistance=35 units; pulmonary vascular resistance=11.5 units			

Donor Selection

It was clear to us that a heart donor could be managed in the same way as a patient donating a kidney or a liver. The same steps that were taken for the kidney transplant would thus be followed in the heart donor, namely:

1. Observance of all the requirements of the law.
2. Care that the transplanted organ was normal.
3. The organ had to be genetically as close as possible to the recipient's tissue.
4. Donor free of any disease that could be transferred to recipient.

Legal Requirements

Before 1952 there was no legal provision for the removal of tissues from bodies of deceased or living persons for transplant purposes. Representations made by various bodies, including the South African National Council of the Blind, led up to the enactment of the Post Mortem Examinations and Removal of Human Tissues Act (30 of 1952, as amended by Act 49 of 1961), which provides for the postmortem examination of certain bodies of tissue for therapeutic or scientific purposes and for the preservation and use of such tissue.

In practice, the law required that the following steps had to be taken:

a. The fact of death had to be certified by two registered medical practitioners, who may not have been members of the transplant team, and one of whom must have been practicing for at least five years since registration. What constituted "death" was left to the discretion of the two doctors concerned.

There was no attempt made to define the moment of death, and the absence of heart beat and respiration was not required, and if the two doctors used the criteria of brain death, it was legally acceptable.

b. Once death was certified, the transplant team could take over the management of the donor and ask for permission for donation in one of three ways:

1. Permission by the donor prior to death.
2. Permission of relative after death.
3. In the absence of donation as per 1 or 2 above (for example, if relatives could not be traced), the district surgeon could give permission if he was satisfied that all attempts had been made to find the relatives.

c. After permission for donation was given, a member of the transplant team further had to get permission from the medical superintendent of the hospital, or his deputy, to remove the donated organ.

Normality of the Donor

This was established (when possible) by a careful evaluation of the donor history of past or present illnesses as established from the family. A cardiologist was then asked to examine the donor and a chest x-ray and EKG were performed.

Normality of the Donor Heart

Decision was made to accept only donors in whom coronary artery diseases were unlikely to be present. Due to the high incidence of this disease in white and mixed-race patients over the age of 40, only donors under the age of 35 were considered suitable.

Patients with preexisting cardiac disease would be turned down and the presence of diabetes and hypertension would also preclude donation. To exclude the presence of cardiac disorders, we would rely mainly on a clinical history from the patient's relatives or his/her own medical practitioner, by clinical examination, by study of chest radiograph, and a 12-lead EKG.

Histocompatibility of Donor Heart

On several occasions before and after the first heart transplant, I heard the statement made that this operation should not be attempted until such time that rejection could be prevented. It is common knowledge that at that time, or even now, 23 years later, this goal could not be achieved. It was, however, possible to take certain precautions so that the immune response would be as mild as possible.

As in the case of the kidney transplant, we determined that there was ABO blood compatibility between donor and recipient and the absence of preformed antibodies as shown by donor lymphocyte recipient-serum crossmatch.

Tissue typing tests were performed (6), but the selection of the donor was not influenced by this result.

Absence of Transferable Diseases

This again was excluded by a careful clinical history and physical examination.

Maintenance of Recipient

As already pointed out, the first recipient was seriously ill and had a very short life expectancy, probably measured in weeks. In later studies we found that the mean survival time of patients who were accepted for cardiac transplantation, but died while awaiting a donor, was 26 days (7).

As the patient was in terminal heart failure and bed-ridden, he was managed as any other patient with severe congestive heart failure, except that he required mechanical removal of edema (with Southey's tubes), which resulted in a chronic, indolent cellulitis of the devitalized left calf. We also treated him for diabetes. The relevant medical therapy before transplantation was:

Digoxin-0.25 mg bd
Prednisone-10 mg bd 3 times per week
Lasix-40 mg bd
Slow-K tabs-2 tds
Librium-10 mg tds
Diabinese-1 1/2 tabs bd
Ethacrynic acid 50 mg 6-hourly
Gentamicin for the infection of his calf

Afterwards, we realized that there were three reasons why this patient would not do well on high doses of steroids: a) his age and severity of illness; b) the presence of active infection; c) his diabetic state

The 2nd of December, 1967

It was a Saturday afternoon, and I was having a nap when Dr. Bosman phoned to tell me that he thought we had a donor; a 24-year-old white female by the name of Denise Davall.

I should mention here that Professor Schrire and I decided that the first patient and donor for heart transplantation should be white South Africans, not because of any problems with the South African authorities, but because we were afraid that if either the patient or donor were black we would be criticized for having experimented on black patients. The first transplant could have been performed two weeks earlier when a very suitable black donor became available.

This turned out to be a wise decision, as one of the first questions I was asked by a British doctor from London on Monday was, "Did you do this operation to improve the bad image of your country overseas?"

Denise Davall was struck by an automobile 1.5 kilometers from our hospital shortly before 4 PM.

4 PM

The donor was admitted to Groote Schuur Hospital with cerebral damage and multiple fractures of the pelvis and lower limbs. Deeply unconscious, her blood pressure was 60/0 mm Hg, CVP - 2 cm H_2O and pulse rate 120/minute. Resuscitation was begun by the multiple injury service. She was seen frequently by neurosurgeons, eventually declared a potential cardiac transplant donor, and admitted to the cardiothoracic ward at 9 PM after the neurosurgeon declared that she was dead.

10 PM

Her blood pressure was 60 mm Hg and she was now being ventilated mechanically via an oral endotracheal tube which intubated a bronchus and was withdrawn in order to lie in the trachea. Further blood transfusions and the administration of calcium gluconate and sodium bicarbonate resulted in a rise of blood pressure to 110 mm Hg and a venous pressure of 3-4 cm H2O. The EKG, as monitored on an oscilloscope, was normal. The necessary permissions and tests as described previously were completed while in the meantime the patient was prepared for surgery.

The 3rd of December, 1967

12:45 AM

The donor was transferred to the operating theater and placed in one of the two operating rooms prepared for the transplant. Artificial ventilation and EKG monitoring were continued. Blood pressure at this stage was 95-100 mm Hg and she was prepared for a thoracotomy and total cardiopulmonary bypass. A disposable oxygenator primed with Ringer's lactate solution was kept in readiness in this theater. My brother Marius and Dr. Terry O'Donovan were put in charge of the removal of the donor heart.

12:50 AM

The recipient was brought to the anesthetic induction room: blood pressure was 130 mm Hg and pulse rate 90/minute. Atropine (0.6 mg) was given intravenously, resulting in the pulse rate increase to 100/minute.

12:55 AM

Anesthesia was induced, an oral endotracheal tube was passed into the trachea, and the patient moved to the operating room next to the donor. He was prepared for open heart surgery like any other patient.

I decided not to scrub at this stage so that I could coordinate events in both rooms. Doctors Hewitson and Hitchcock were in charge of starting the operation on the recipient.

1:30 AM

The operation commenced with the right groin incision to expose the femoral artery and the saphenous vein. The vein was cannulated to monitor venous pressures and used to inject any intravenous drugs.

1:40 AM

The thoracotomy commenced and the patient's heart exposed through a median sternotomy incision and the heart prepared for cardiopulmonary bypass. Heparin was given and the femoral artery cannulated.

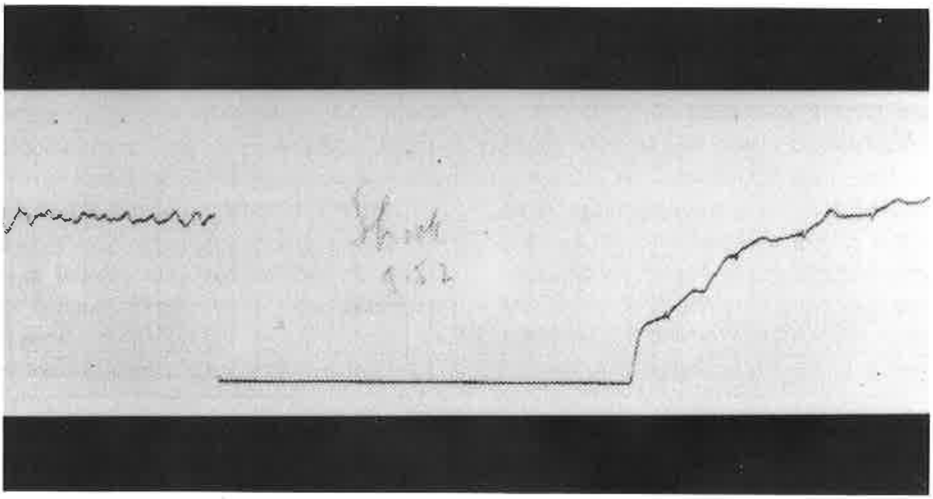
2:20 AM

I walked across to the donor and disconnected the respirator. The donor was heparinized.

2:32 AM

The donor heart went into cardiac arrest, and only at this stage did Dr. O'Donovan and my brother start to open her chest. They were instructed to connect the donor's heart to the oxygenator as soon as possible. This was done by placing a catheter in the ascending aorta for arterial return and a single venous catheter in the right atrium through the appendage for venous return. Bypass and cooling were started. A vent was placed in the left ventricle, via its apex, and put onto slow suction to prevent distention of the atonic left ventricle. General body cooling was continued until the mid-esophageal temperature had dropped to 26°C, as the kidneys were also to be protected for use in a transplantation procedure in another hospital. When the mid-esophageal temperature had reached 26°C, the aortic cannula was adjusted so that it pointed toward the aortic valve. The flow was

Heart team December 1967, photographed after first transplant.



E.C.G. showing the first few beats of the transplanted heart.

then crossclamped so that only the myocardium of the donor's heart was perfused. The heart was cooled down to 16°C and, leaving the catheters in the aorta and left ventricle, it was removed and placed in a bowl containing Ringer's lactate solution at 10°C.

2:32 AM

Cardiopulmonary bypass and cooling of the recipient were begun by connecting the patient to a bubble oxygenator primed with citrated blood diluted with plasmolyte-B solution. This was done by placing a catheter in the femoral artery and two catheters for venous return introduced via the atrial appendage into the venae cavae. During insertion of the cannula into the right common femoral artery, we noticed that this vessel was atherosclerotic. After seven minutes of bypass it was noted that the arterial line pressure had risen to 300 mm Hg. Accordingly, a cannula was inserted into the ascending aorta and the bypass was discontinued momentarily while the arterial line was disconnected and reconnected to the cannula in the ascending aorta. Bypass was recommenced after three minutes.

3:01 AM

The donor heart arrived in the patient's operating room. Perfusion of the heart was recommenced immediately (0.4 l/minute) by connecting the arterial cannula to a coronary perfusion line, and as soon as the aorta had filled to displace the air, it was clamped distal to the perfusion cannula so that the coronary arteries would be perfused. The heart was vented continuously during this procedure, and a period of four minutes had elapsed between cessation of perfusion in the second operating theater. The patient's heart was now excised and the donor heart connected in exactly the same way as we had done in the animal laboratory.

5:43 AM

The transplant was completed and rewarming started.

5:52 AM

With esophageal and rectal temperatures of 35.4°C and 28.1°C, respectively, the heart was defibrillated by a single shock.

6:06 AM - 6:13 AM

Three trials of unassisted circulation were made. After the third attempt, the patient maintained an adequate blood pressure. The transplanted heart was carefully inspected for bleeding from the suture lines. The heparin was neutralized with protamine. Drains were placed in the pericardial sac and mediastinum and the pericardium closed. I left the closure of the chest to Drs. Hewitson and Hitchcock.

While my brother Marius and I were sitting in the tearoom, we realized that we had not yet informed the head of the hospital about the operation, so I phoned Dr. Burger, the Chief Medical Superintendent, and told him that we had done a transplant. He was not impressed that I woke him so early to give him the news as he thought that I was referring to the animal research. However, when I told him that this operation was done on a patient, he wished me the best of luck.

8:30 AM

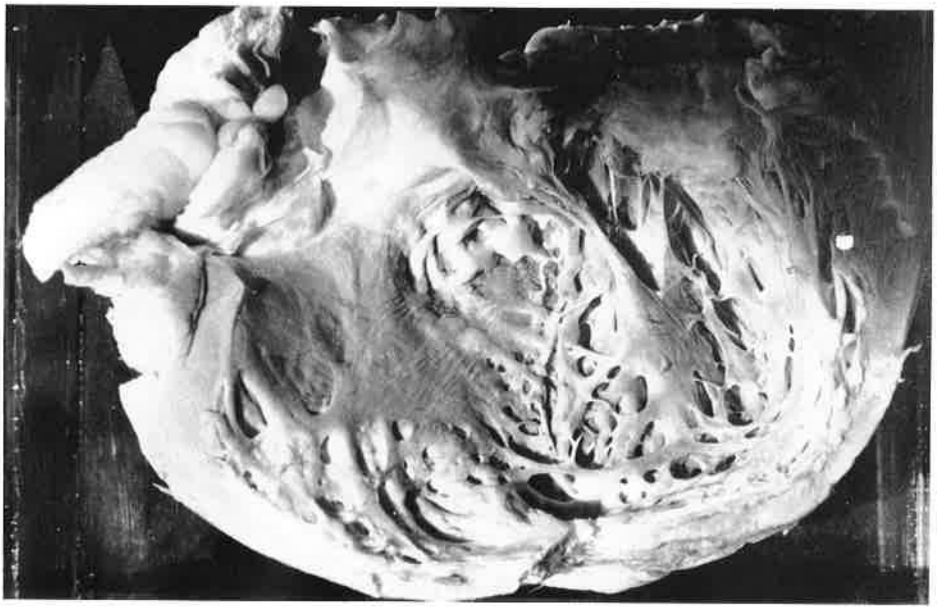
Anesthetic was discontinued, and the patient was returned to a specially prepared ward and placed on a ventilator. The concentrated postoperative care was directed towards maintaining a satisfactory cardiac output, suppressing the immunological reaction, and preventing infection.

I left the hospital at about 9 o'clock that morning, and it may surprise you to learn that there was not a single member of the media waiting for me - no photographers, no reporters, and no television cameras. This was probably because we did not announce our intentions of doing the operation or that the operation was being performed that night. In fact, not a single photograph was taken during surgery.

When I drove back to my home, I turned on the car radio, and a short report in the news bulletin stated that the first

Louis Washkansky with Professor Barnard five days after the transplant.

L. to R. Dr. M.C. Botha, Dr. B. Bosman, and Prof. C.N. Barnard.



Washkansky's own heart.

Barnard on "Face the Nation" with Dr. M. deBakey and Dr. A. Kantrowitz.

human-to-human heart transplant was performed by a team of doctors at Groote Schuur Hospital that night. Soon after I arrived home, I received a phone call from a friend stating that he heard the news bulletin and that if the media did not recognize my contribution during the next week, he would write a letter to inform them! As previously stated, we were quite surprised and not prepared for the massive media interest in this event.

Our patient's immediate postoperative progress was uneventful: He maintained good circulation and passed plus/minus 6 liters of urine over the next 24 hours. At 9 AM on the morning of the 4th of December, the patient was weaned from the ventilator and placed in an oxygen tent, and at 10 AM the nasal endotracheal tube was removed. Mr. Washkansky was now able to talk for the first time. I asked him whether he knew what had happened. He replied, "You promised me a new heart...I assume you kept your promise."

In the next few days we were able to observe the response of a patient who was in terminal congestive heart failure and who had received a normal heart, as in our research we always transplanted to a normal canine recipient. The improvement was absolutely amazing. Within two days, the patient lost all evidence of left and right heart failure. We realized that if a successful heart transplant were performed, the patient would be able to return to virtually a normal life and would not be an invalid. In order to prevent infection and to suppress the immunological reaction, we followed the same procedure as we did in the kidney transplant.

The following parameters were studied to detect any evidence of threatened rejection of the heart: a) the leukocyte response in the blood stream; b) deterioration in cardiac output; c) change in the serum enzyme levels which could indicate myocardial damage; d) changes in the voltage of the R wave of the electrocardiograph.

We treated anticipated rejection the same way Dr. Hume in Richmond did; with steroids, commencing on the day of operation with intravenous hydrocortisone (500 mg) administered over 24 hours, in addition to 60 mg prednisone administered orally. The hydrocortisone dosage was gradually reduced by 100 mg daily while the prednisone dosage was maintained at 60 mg/day. The heart was irradiated locally, using a 1 curie source of cobalt, starting with a dose of 100 rads on day 3, then 85 rads on day 4, and 200 rads on days 5,7, and 9, given in the radiotherapy department. Initially, 150 mg azathioprine was administered daily through a nasogastric tube; as soon as urinary function improved, this was increased to 200 mg.

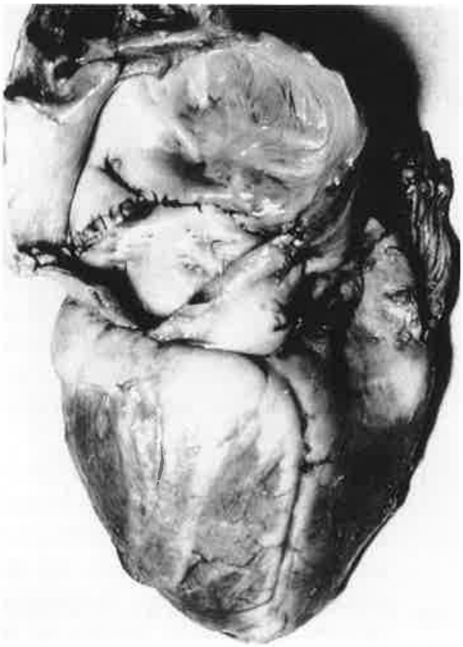
Threatened rejection was treated by daily administration of 200 mg prednisone and 200 mg actinomycin C for three days. The dosage of prednisone was gradually reduced.

Prevention of Infection

Inasmuch as absolute sterility of the patient's environment is not possible, the following preventative measures were adopted:

1. Preoperative period
   a. Patient. The patient was washed daily with hexachlorophene soap. Swabs were taken from the skin, nose, throat, mouth, and rectum and examined for the possible presence of potential pathogens, especially yeasts, Pseudomonas aeruginosa, klebsiella species, beta-hemolytic streptococci, and staphylococci. Antibiotic sensitivities of these organisms were determined where possible. Any obvious septic lesion was treated vigorously.
   b. Staff. Nurses and medical staff who were to handle the patient postoperatively had swabs taken from the nose, mouth, throat, and rectum for bacteriological examination to determine whether they were carriers of any potential pathogens.

Barnard photographed with the Pope in 1968.



First transplanted heart, autopsy.

Table 2. Recipients

No.	Sex	Age	Cardiac Disease	Other Complications
1	M	53	Ischemic heart disease	Diabetes mellitus
2	M	58	Ischemic heart disease	Atherosclerosis
3	M	52	Cardiomyopathy	
4	M	63	Rheumatic heart disease aortic valve replacement	Mental depression Squamous epithelioma of scalp
5	F	37	Rheumatic heart disease aortic and mitral valve replacement	

c. Room. A room was set aside in the unit, which was thoroughly cleaned in the following manner:
   i. gaseous disinfection under bacteriological control;
   ii. thorough washing of all walls and floor with a phenolic disinfectant, using boiled cleaning utensils;
   iii. thorough washing of the bed with liberal amounts of the correctly diluted phenolic disinfectant;
   iv. autoclaving of the mattress which was then covered in plastic, and autoclaving of the pillows;
   v. flushing of the wash-basin three times daily with a suitable dilute phenolic disinfectant.

d. Apparatus. Any apparatus to be used near or on the patient was carefully checked for cleanliness. This applied particularly to the oxygen tent, the suction apparatus, and the Bird respirator.

This apparatus was dismantled as completely as possible and thoroughly cleaned mechanically, then all parts which could be autoclaved or boiled were so treated. Parts which could not be boiled or autoclaved were treated by gaseous disinfection, or a phenolic disinfectant. Particular attention was given to any humidifying unit. The water in this unit was changed daily, and the water container was boiled at the end of each day, pre- and postoperatively.

2. Postoperative Period

The patient was transferred to the specially prepared room. All staff attending the patient wore caps, masks, canvas overshoes, and sterile gowns and gloves, as for any sterile procedure. After any form of attention to the patient, the gloved hands were rinsed in the iodophor disinfectant and dried on disposable paper towels.

The patient's sheets and cotton blanket were changed twice daily, taking due care not to disturb the air excessively while doing this. The floors were mopped twice daily with a phenolic disinfectant. The mops were rinsed in hot water and dried before use.

In addition, the following measures were taken:

a. Patient. Every second day, swabs for bacteriological examination were taken from the nose, throat, mouth, and anus to assess the presence of potential pathogens, or a change in bacterial flora.

   All venepunctures, intravenous therapy sites, and injection sites were treated as for a sterile surgical procedure. Daily blood cultures were performed. Careful attention was given to the perineum and scrotal region. These areas were dusted daily with hexachlorophene and mycostatin powder.

b. Staff. Nose, throat, mouth, and rectal swabs were taken for bacteriological investigations every week to assess the presence of any potential pathogens. Antibiotic treatment was introduced as required.

The diabetes was controlled as for any diabetic patient who had undergone major surgery by means of frequent urine testing for sugar and ketone bodies, and regulating

Table 3.

Patient	Age	Survival Days	Results
1	53	18 days	Died pneumonia
2	58	18 months	Died chronic rejection
3	52	20 months	Died stomach cancer
4	63	64 days	Died pneumonia/nephritis
5	37	12.5 years	Died chronic rejection

a dosage of soluble insulin accordingly. This aspect did not present any particular problems.

The patient improved steadily until the ninth postoperative day when we recognized that something was going wrong. He was listless and wanted to be left alone. On the eleventh postoperative day he developed symptoms and signs of pneumonia and died on the eighteenth postoperative day. We isolated pneumonia caused by Pseudomonas aeruginosa and klebsiella - the same organisms as obtained from the calf infection.

The autopsy performed 1.5 hours after death revealed a striking absence of congestion of the liver, and there were no morphological indications of cardiac dysfunction. The pneumonic lesions were widespread in both lungs, and there were no indications of rejection (8).

Despite our lack of experience in those early days, the results were not as bad as most people suggested. Three of our first 5 patients (Table 2) survived more than 18 months, and one died 12.5 years after surgery (Table 3). The seventh patient, transplanted on May 10, 1971 is still alive without a retransplant and doing extremely well. I believe I am correct in assuming that he is the longest surviving heart transplant patient.

In my mind, two events contributed to the excellent results obtained today: the introduction of transvenous endomyocardial biopsy in 1972 and cyclosporine in 1980.

REFERENCES

1. Demikhov VP. Experimental transplantation of vital organs. Translated from the Russian by Haigh B, New York, 1962.
2. Cass MH, Brock R. Heart excision and replacement. Guy's Hosp Rep 1959; 108:285.
3. Lower RR, Shumway NE. Studies on orthotopic homotransplantation of the canine heart. Surg Forum 1960; 11:18.
4. Barnard CN. What we have learned about heart transplants. J Thorac Cardiovasc Surg 1968; 56:457.
5. Schrire V, Beck W. Human heart transplantation - the pre-operative assessment. S Afr Med J 1967; 41:1263.
6. Botha MC. Human heart transplantation - the tissue typing tests. S Afr Med J 1967; 41:1265.
7. Cooper DKC, Charles RG, Beck W, Barnard CN. The assessment and selection of patients for heterotopic heart transplantation. S Afr Med J 1982; 61:575.
8. Thompson JG. Provisional report on the autopsy of L.W. S Afr Med J 1967; 41:1277.

CURRICULUM VITAE

Christiaan Neethling Barnard

PERSONAL

Born:	November 8, 1922; Beaufort West, Cape Province

EDUCATION

1940	Matriculated 1st Class Beaufort West High School
1946	University of Cape Town, M.B.
1948-51	Houseman at Groote Schuur Hospital, Cape Town; then private practice, Ceres, Cape Province
1951-53	Senior Resident Medical Officer, City Hospital, Cape Town Registrar, Professor J.F. Brock's Firm, Department of Medicine, Groote Schuur Hospital
1953	University of Cape Town, M. Med (Medicine)
1953	University of Cape Town, M.D. Thesis "The Treatment of Tuberculous Meningitis"
1956	Registrar Department of Surgery, Professor J. Erasmus's Firm Recipient, Charles Adams Memorial Scholarship, and Dazien Foundation Bursary for 2 years' study in the United States
1956-58	University of Minnesota, Trained in Cardiothoracic Surgery (with Dr. C.W. Lillehei and Dr. R.L. Varco) Department of Surgery (under Professor O.H. Wangensteen). Thesis "The Aortic Valve - Problems in the Fabrication and Testing of a Prosthetic Valve"
1958	University of Minnesota, M.S. (Master of Surgery) Thesis "The Aetiology of Congenital Intestinal Atresia"

POSITIONS

1958	University of Cape Town and Groote Schuur Hospital, Specialist Cardio-Thoracic Surgeon, lecturer and Director of Surgical Research under Professor J.H.Louw
1961	Head of Cardio-Thoracic Surgery Department at the teaching hospitals of the University of Cape Town
1962	Associate Professor, University of Cape Town
1968-83	Head of Cardiac Research and Surgery, University of Cape Town
1972	Professor in Department of Surgery, University of Cape Town
1983-	Professor Emeritus, University of Cape Town
1985-87	Scientist in Residence, Baptist Medical Center, Oklahoma City

AWARDS

Honorary Fellowship of th American College of Surgeons - Resigned 1986

Honorary Fellowship of the American College of Cardiology

Honorary Fellowship of the New York Cardiological Society

Honorary Fellowship of the University of Cape Town

Honorary Doctorate of Medicine - Pahlavi University of Shiraz, Iran
Honorary Doctorate of Science - Gama Filho University, Rio de Janeiro
Honorary Doctorate of Science - Collegii Spei, Holland, Michigan
Honorary Doctorate of Science - Florida Southern College
Honorary Doctorate of Science - University of Cape Town
Honorary Membership of the Societe de Medicine de Paris
Honorary Membership of the Pan American Medical Association
Honorary Membership of Lions International
Honorary Membership of Montreal Clinical Society
Honorary Membership of Research Centre, Lagoa State Hospital of Rio de Janeiro
Honorary Membership of the Venezuelan Society of Cardiology
Honorary Membership of the Order of the Knight Hospitalier of St. Thomas d'Acre
Honorary Membership of the Dental College of Lima
Honorary Membership of the the Brazilian College of Surgeons
Honorary Membership of the Cardiology Foundation and Society of the Dominican Republic
University of Pretoria - Gold Medal
American College of Cardiology, Silver Medal
American College of Cardiology, Diploma Award
Sydney University Medical Society - Medal
Venezuelan National Academy of Medicine - Diploma of Honour
University of Caracas - Diploma Award
Rijks University, Leiden - Presentation of two Plaques
Czechoslovakian University - Medal of Gregor Mendel Award
University of Purkynianaes Bkunesis - Diploma Award
University of the Philippines Heart Institute and Transplant Foundation - Medal
Albert Einstein College of Medicine - Medal
Lombardi Medical Academy, Milan - Medal
College of Surgeons of Ireland - Silver Medal
Pasteur Institute - Medal
1977 St. Boniface General Hospital Research Foundation, Winnipeg - International Award
University of Uruguay - Honorary Doctorate
Golden Heart Medal - Philippines
Golden Cross of the Etoile Union Civique des Elites Francaises - France
Hendrik Verwoerd Medal - South African Republic
Order of the Republic "Andres Bello" - Venezuela Republic
Silver Cross - Dominican Republic
Order of Merit - Ecuador Republic
Order of the Sun - Peru
Member of the Order "Hipolito Unanuo" - Peru

Honor Merito Salud Publica - Paraguay Republic

Diploma de Onoare with Medal - Romania

Cross of the National Cedar Decoration - Lebanon

Blue Cross Award - Spain

The Grand Cordon of the Order of Al-Kawkab Al-Urdini (First Class) - Jordan

Cross of Grand "Ufficiale in the ordine "al Merito della Republica Italiana" - Italy

The Decoration of the Commander of the Order of the Phoenix - Greece

Order of Brilliant Star with Violet Grand Cordon, Star Medal, Three Certificates and Violet Sash - Republic of China

Freedom of Beaufort West, Cape Province, South Africa

Freedom of the Republic of Vincento Lopez

Freedom of the City of Cape Town

Freedom of the City of Sao Paulo

Freedom of the City of Mayaquez

Freedom of the City of San Juan

Freedom of the City of Winterhaven

Freedom of the City of Flint

Freedom of the City of Santo Domingo

Honorary Citizenship of Memphis, U.S.A.

Honorary Citizenship of Chatillon-les-Dombes, France

Honorary Citizenship of Carpineta, Rome, Italy

Honorary Citizenship of Birmingham, U.S.A.

Honorary Citizenship of Riberao Proto, Brazil

Honorary Citizenship of New Orleans, U.S.A.

Honorary Citizenship of Winnipeg, Canada

Honorary Citizenship of State of Guanabara, Brazil

Honorary Citizenship of the Island of Oinoussai, Greece

Golden Spur of Florence

Pope Paul VI - Medallions with inscribed book

The Seal of the President - Philippines

Kennedy Foundation Award

Public Tribute of Mayor John V. Lindsay - City of New York

Document of Welcome by Nelson A. Rockefeller - Governor of New York

Plaque - Government of Quebec

Certificate of Recognition by Pierre Trudeau - Prime Minister of Canada

Diploma and gold medal - Chile

Dag Hammarskjoeld Peace Prize

Dag Hammarskjoeld International Prize, also the 15th Anniversary Prize

International Federation of Arts, Letters and Science, France- Diploma of Honour
Knights of Humanity Award and Diploma of Honour - Italy
Academie Dolle Scienze di Roma - Diploma Solenne and Certificate of Honour
Academia Artistica Internazionale, Italy - Award of Honour
La Madonnina International Prize for Science
International Cardiological Symposium, Naples - Diploma with gold scalpel
World Association of Military Surgeons - Award of Honour
Medical Association of South Africa - Gold Medal
South African Academy of Arts and Science - Christo Voryers Award
Cape Town Chris Barnard Fund - Gold Medal
South African Cape Provincial Council - Medal
Gold Medal inscribed with Hippocratic Oath - France
National Federation of Blood Donors - Medal and Scroll
Lyons Administration Hospital, France - Medal
New York Cardiological Society - Award of Honour
Stritch Award - Plaque and Medal
Venezuela Fotrasalud Award
Lodovico Mina - Humanitarian Award
Brazil Ipase Hospital dos Servidorae do Estado - Certificate Honoris Causa
Premio Via Veneto Literary Award for "One Life"
South African Medical Journal - Blignault Medal for best article of 1975
Bombay Medical Research Centre -Medal of First Tropical Conference on Surgery
Bogata La Fundacion Cardio Infantil - Diploma
Bogata Certificado De Amparo - Certificate
Colombia Rotary International "Socio Honorario " Diploma
Premio Internazionale " San Valentino D'Oro", Terni, Italy
Eugan Moog Foundation of Germany and the USA - Cross of Merit and Certificate of Honour

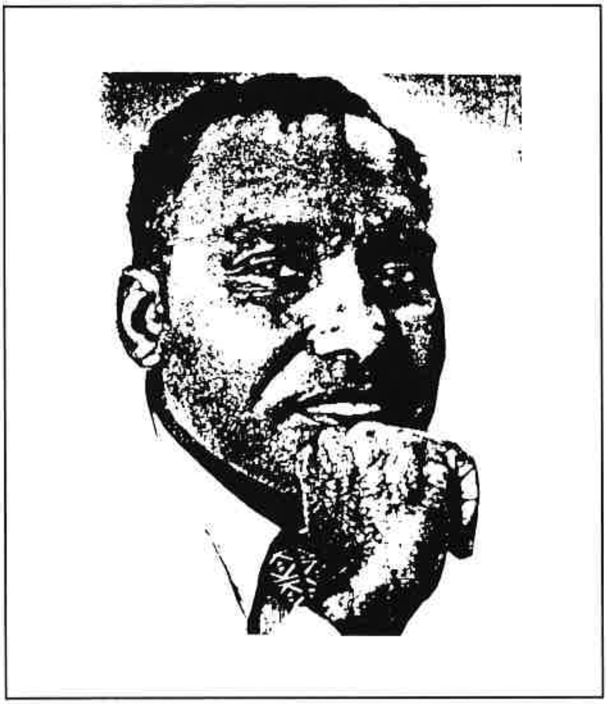
PUBLICATIONS

14 books

Samuel Lee Kountz
1930 - 1981

As remembered by Folkert O. Belzer
and Khalid M.H. Butt

Samuel L. Kountz



Samuel L. Kountz

A REMINISCENCE OF DR. SAMUEL KOUNTZ

by Folkert O. Belzer

Samuel Lee Kountz was born October 20, 1930, and was raised in Lexa, Arkansas, a farming community 50 miles southwest of Memphis, Tennessee, with a population of 500.

His father was a Baptist minister, and his grandmother was born a slave. He attended the all-black Arkansas Agricultural, Mechanical and Normal College in Pine Bluff, from which he earned a Bachelor of Science degree in 1952, and was third in his class.

He next studied chemistry at the University of Arkansas, which awarded him a Master of Science degree in 1956.

Sam Kountz was the 10th black student admitted to the University of Arkansas School of Medicine, and he graduated in 1958. He was accepted for internship at the San Francisco County Hospital on the Stanford service, and when the medical school moved from San Francisco to the main university campus at Stanford, Sam was invited to come along.

During the next three years, as Assistant Resident in Surgery, he became interested in renal transplantation, primarily because of the work of Dr. Roy Cohn. Cohn and Kountz's first paper together was published in 1962.

That same year, Sam was awarded a scholarship for a year at the Hammersmith Hospital in London, where he worked with another pioneer in transplantation, Dr. W. J. Dempster. They published eight studies during this year.

After a visit to Egypt, where he demonstrated renal transplantation surgery, he returned to Stanford and finished his Chief Residency in 1964. He was appointed Assistant Professor of Surgery at Stanford in 1966 and became active in clinical kidney transplantation.

The following year, Sam was recruited to join the faculty of the University of California in San Francisco. I can still remember the first time I met Sam.

I was working in my laboratory, a small, wooden building behind the hospital, and Dr. J. Englebert Dunphy brought Sam over so we could meet.

From this introduction, an immediate friendship developed, a friendship that lasted not only for the five years we worked together in San Francisco but continued until his unfortunate early death.

Sam and I were appointed Co-Directors of the transplant service, an arrangement, which, interestingly, worked amazingly well. Sam was concerned with running the administrative duties of the transplant service, and this allowed me to spend my time in the surgical research laboratory. But we shared the clinical service equally and always made rounds together seven days a week.

In those days, we also shared organ procurement, and, together with Bob Hoffmann, we covered over 25,000 miles in a van donated by our patients obtaining kidneys throughout northern California.

Sam's main research interest at that time was immunosuppressive therapy and tissue typing. To my knowledge, Sam was the first to use high doses of Solumedrol in the posttransplant period; he initially gave it intraarterially but subsequently switched to intravenous use.

He started the first clinical study on living-unrelated kidney transplants based on HLA matching. He also worked many years trying to develop an abbreviated, mixed-lymphocyte culture reaction, with the idea of using it in clinical cadaver renal transplantation.

During Sam's five years of tenure at the University of California, the renal transplant program became one of the largest in the world and published more than 70 papers.

Sam's greatest attributes, however, were that he was a tireless worker, an eternal optimist, a compassionate physician and surgeon, and a warm, joyous human being. Patients loved him and felt secure under his care. It was no surprise that Sam was declared Man of the Year by the Kidney Foundation of Northern California in 1969.

In 1972, Sam was recruited to New York and appointed Professor and Chairman of the Department of Surgery at the State University of New York, Downstate Medical Center in Brooklyn, a position in which he again flourished.

I remember very well my visit to Downstate Medical Center when Sam invited me to be a Visiting Professor in 1973. As we walked the corridors of the Kings County Hospital, he greeted everyone we met by his or her first name, whether they were physicians, janitors, medical students or nurses. He was obviously respected and admired, but, most important, he was clearly everyone's friend.

He rejuvenated the transplant program at Downstate and continued his writing; by 1977, the year of his illness, he had published more than 175 papers and assumed many leadership roles in academic medicine.

While still in San Francisco, he was appointed President of The Society of University Surgeons, and while in New York, he received three honorary doctoral degrees, including Doctor of Law from his alma mater, The University of Arkansas at Pine Bluff. A building on the Fayetteville campus was named the Kountz-Kyle building.

In May 1977, after a scientific visit abroad, he contracted an illness that resembled infectious encephalitis, from which he never recovered. He was sick for a long time, first in the hospital, and subsequently at home where he was cared for by his loving wife Grace. Sam died late in 1981.

Although he obviously enjoyed the Chairmanship at Downstate, I had always thought that, for Sam, this was an interim period before a subsequent career in politics and health-care delivery. Sam was an astute politician, and had his life not been cut short, I am sure he would have become Secretary of Health or Surgeon General.

Although Sam was stricken at the peak of his career, he lived a full life as a devoted husband and father, as a physician and surgeon whose work was also his hobby, as an individual who stimulated everyone around him, and as a role model for many.

We continue to miss him.

DR. SAMUEL KOUNTZ: A REMEMBRANCE
by Khalid M.H. Butt

Samuel Lee Kountz was born on October 20, 1930 to Reverend and Mrs. J.S. Kountz of Lexa, Arkansas, a farming community of approximately 500 residents located 50 miles southwest of Memphis, Tennessee. His father was a Baptist Minister and his grandmother was born a slave.

Dr. Samuel Kountz' rise to greatness from such humble beginnings in Lexa may appear miraculous to some, but for those who knew him well, it was a natural sequel to his innate intelligence and ability to work extremely hard.

His early education was in public schools. At age 14 he left home for the Baptist Academy and stayed in the Baptist boarding school for three years.

In 1948 Samuel Kountz entered Arkansas Agricultural Mechanical and Normal College in Pine Bluff and earned his Bachelor of Science degree in 1952 ranking third in a class of 178 students. On July 15, 1948, on his admission application, he wrote, "I plan to be one of the best students that has ever attended AM&N College. For my future I hope to be one of the best doctors in the world in my day and time. I believe that it is my calling and highest ambition and I'm going to make every effort to make it a success." He carried out that commitment throughout his life.

While at Arkansas AM&N he escorted Senator William Fulbright on a tour of the college. Senator Fulbright, learning that Sam Kountz wanted to seek admission to one of the two negro medical schools, advised him to try the University of Arkansas which up to that time was an all-White university. He entered the University of Arkansas Graduate School and was Awarded a Master of Science in 1956. He later remarked, "It would have been a tragedy if I had not had that scientific grounding." He was a teaching assistant in the Department of Chemistry from 1952 to 1954.

In 1954 Sam Kountz entered the University of Arkansas School of Medicine, the tenth black student to be admitted to this school, and he graduated in 1958.

Through the National Intern Matching Program, Dr. Kountz was appointed to the Stanford service at San Francisco General Hospital in 1958. Thus, Dr. Kountz went west with the private resolve "to do something as well or better than anyone else in the world." When the medical school moved from San Francisco to the main university campus at Stanford, Dr. Kountz was invited to continue his surgical residency there. During the next three years of assistant surgical residency at Stanford, Sam Kountz developed a passionate interest in the science and practice of renal transplantation. He was inspired by Dr. Roy Cohn, a pioneer transplant surgeon and his mentor. Years later Sam Kountz recalled how he and Dr. Cohn would go over to the experimental surgery laboratory and perform transplants in dogs. Very early in his laboratory experience Dr. Cohn removed a rejected renal allograft from a dog and placed the cut surface of this massively swollen, edematous, and hemorrhagic graft next to a normal dog kidney. Turning to Sam Kountz, he said that the problem of homotransplantation of kidneys and the challenge was to first work out in detail the mechanisms of rejection of the allografts and then to find ways of modifying those biological responses to avoid the failure of the graft. This is how Sam Kountz started on a quest that carried him to many countries and continents. Drs. Cohn and Kountz wrote their first paper together in 1962. In the same year he was awarded the Bank of America Giannini Fellowship to go to the Royal Postgraduate Medical

School, Hammersmith Hospital, London. During this British sojourn, Dr. Kountz worked with a brilliant transplant pioneer, Dr. William James Dempster. Together they wrote eight scientific papers and developed evidence that mononuclear cells in kidney grafts primarily attacked the postglomerular capillaries interfering with the circulation through the organ, and the resulting ischemia contributed to the picture of rejection. This concept, developed primarily from morphologic studies of the allografts by light and electron microscopy, was amply confirmed by other researchers.

In 1963 Sam Kountz returned to Stanford and completed his surgical residency by 1965 when he was appointed Instructor in the Department of Surgery and the following year promoted to Assistant Professor. In 1965 he became a Visiting Fulbright Professor to the United Arab Republic for three months, to work at the Medical Research Institute in Alexandria. During this stay, Dr. Kountz is credited with performing the first human renal transplantation in Egypt. In 1967 John Najarian left the University of California at San Francisco to become the Professor and Chairman of the Department of Surgery at the University of Minnesota. Dr. J. Englebert Dunphy (Chairman at UCSF) succeeded in moving Dr. Kountz from Stanford to UCSF where he was appointed Associate Professor of Surgery and Director of the Renal Transplantation Service.

Over the next five years, close collaboration between Dr. Samuel Kountz and the Co-director of the Renal Transplant Service, Dr. Folkert O. Belzer (currently Professor and Chairman, Department of Surgery, University of Wisconsin, Madison) resulted in an exemplary profusion of clinical and laboratory research, application of laboratory findings in the clinics, and the establishment of a model renal transplantation service that excited the envy of many of the leaders of the time. Belzer and Kountz developed the extracorporeal hypothermic pulsatile perfusion preservation with plasma-based acellular perfusate. With a portable model of Belzer's machine, they would travel all around northern California to collect cadaver donor kidneys for transplantation at the Moffit Hospital. The Medical Center developed or refined the techniques of histocompatibility testing including transplantation antigens (HLA, mixed-lymphocyte cultures, kidney cell crossmatch, etc). Dr. Kountz is also credited with the discovery of the beneficial effect of intravenous Methylprednisolone that he initially injected intraarterially to later find that intravenously administered Solumedrol injection was also equally effective.

In 1972 Sam Kountz was promoted to the rank of Professor of Surgery at the University of California, San Francisco. As the Chairman of the local organizing committee, he hosted the Fourth Clinical Congress of the Transplantation Society and emerged as a superstar in the galaxy of transplantologists. His advocacy of conservatism in immunosuppression and accepting failure of the graft and retransplantation made sense to many transplant surgeon/patient advocates around the world. Belzer is and Kountz' contribution in cadaver organ preservation not only made it possible for more organs to be evaluated and transplanted to benefit many more patients but also reduced the urgency of cadaver donor renal transplants and made it a semi-elective procedure.

In 1972 Dr. Samuel Lee Kountz accepted the position of Professor and Chairman, Department of Surgery, State University of New York Health Science Center at Brooklyn which, at that time, was called Downstate Medical Center. He was also appointed Surgeon-in-Chief of the Kings County Hospital Center. This five-year period from 1972 to 1977 allowed him to use his extraordinary potential as an inspiring leader. This was best elucidated by Dr. Gerald Shaftan, Professor of Surgery and Chief of Trauma Service at Downstate

Medical Center, and quoted by Professor Leslie Brent in his dedication at the Sixth International Congress of the Transplantation Society. "We, especially the older members of the Department of Surgery, look to Sam as a sort of Messiah to lead us out of the wilderness. In discussing this with Dr. Butt this morning, I compared Sam with John F. Kennedy. During Kennedy's term of office many saw the United States as moving rapidly into an era in which it might become a modern Camelot filled with order and tranquility in which everybody would be happy and prosperous. Sam was our King Arthur and like Kennedy he was struck down before his noble objective could be achieved. He was a great leader, a fine researcher, a superb surgeon, a strong colleague, a good friend, and most of all a warm individual with strong family ties, devotion to his wife and children, and to his adoptive family (and he adopted all of us even if most of us were inherited); a splendid teacher, a wise counselor, an astute politician, a shining beacon to his Black brethren for whom he represents the pinnacle to which an individual can climb in knowledge, training, and skill, he was an inspiration to us all and we miss him deeply." To this glowing testimonial, Professor Brent added that Sam's reputation as a surgeon and scientist "far transcends the boundaries of Brooklyn and, indeed, of the United States."

In 1974 Sam Kountz was the elected President of the Society of University Surgeons, probably one of the highest honors bestowed on an academic surgeon in the United States.

Sam Kountz was widely sought after as a lecturer and visiting professor. He went as a visiting professor to Harvard Medical School and the Brigham and Womens Hospital as a guest of Dr. Francis D. Moore, in the oldest continuing tradition of "Visiting Surgeons-in-Chief Pro Tempore" in the United States started by Harvey Cushing about 1914. Dr. Moore recalled that as a visiting professor Sam did a superb job. He was inspiring to students. His scientific lectures and laboratory rounds were an unforgettable experience for all. Sam Kountz went to South Africa as a guest of the South African Surgical Research Society and as a visiting professor of the University of Cape Town. This became the last of his many visits abroad. Some at home had advised him not to go to South Africa, but his attitude was that there was more to be gained from contact than from isolation.

On his return from South Africa, Sam Kountz was stricken by a mysterious illness that left him physically and intellectually incapacitated for over four years. He died at the age of 51 on December 23, 1981 at his home in Kings Point, New York.

During the services at the Downstate Medical Center, Dr. Calvin H. Plimpton, President of the institution, remarked, "Sam was famous when he came here but he added to the fame he bore. He brought a grandeur, a dignity, a sense of style, a new and inspirational dimension. In his life he crossed some new finish lines, that he just got out of the habit of stopping. He never finished. All those finish lines were just steps upwards and onwards. And even now, though he has crossed what we think is the final finish line, he is still running. His inspirational heart is still beating. He hasn't and he isn't finished."

As a physician, Sam Kountz did his very best for each individual patient he cared for. His intellectual realm, however, was far beyond that. He was, indeed, a visionary and a thinker, always planning and executing schemes to mold public opinion and help develop public policy that would be beneficial to the great masses of people. He was never one to shy away from challenges and was frequently daring where most of the rest might be intimidated. Very early during his tenure as the Chairman of the Department of Surgery in Brooklyn, he recognized that there were many apprehensions and misconceptions about transplantation in the community at large. When Sam Kountz and I did a live telecast of a living-related donor kidney transplant for NBC's Today Show in 1974, in a very unmistakable manner he was able to educate the television audiences.

Sam Kountz received many honors here at home and abroad. In 1964 he received the Young Investigators Award from the American College of Cardiology, in 1967 the Lederle Medical Faculty Award. In 1969 he was selected for the Man of the Year Award by the Kidney Foundation of Northern California. In 1970, the University of San Francisco conferred upon him an honorary Doctor of Humane Letters degree. In 1974, he was awarded a Doctor of Laws from the University of Arkansas. In 1975 he was conferred a Doctor of Laws honorary degree from Howard University.

In 1977 AM&N College, Pine Bluff, dedicated a building as the Kountz-Kyle Building. A building at Harlem Hospital in New York was named Kountz Pavilion. The section of the hospital housing the transplantation service at the Downstate Medical Center has been named Samuel Lee Kountz Transplantation Service that I proudly directed for 12 years after the illness and subsequent demise of Samuel Kountz. The NAACP has established an award in his name to be given annually to an outstanding student in science. The Department of Surgery at SUNY Health Science Center at Brooklyn has established an annual Samuel L. Kountz Honor Lecture and the first lecturer was Dr. J. Englebert Dunphy. The Sam Kountz Award for Clinical Excellence in surgery was established for the graduating seniors of Downstate Medical Center. The Seventh International Congress of the Transplantation Society in 1978 in Rome, Italy was dedicated to Samuel Kountz. In 1985 the First International Symposium on Renal Failure in Blacks, held under the aegis of Howard University in Washington D.C., was dedicated to the memory of Samuel Lee Kountz.

The scientific organizations in which Dr. Kountz held membership and positions of leadership are too numerous to list in their entirety, but they include Alpha Omega Alpha, American Association for Advancement of Science, American College of Surgeons (Governor, 1975-78), American Society of Transplant Surgeons, American Surgical Association, Surgical Biology Club III; Transplantation Society, Society of the University of Surgeons (President, 1974-75). He was on the Editorial Boards of *The Kidney*, *The Journal of Hypertension and Renal Disease*, *The New York State Medical Journal*, and *Surgery*.

Dr. Kountz was a prolific writer. During his career, he authored and co-authored more than 200 scientific articles, book chapters and reports. It is the memorialization of his work and writings through which his name will live long after the buildings named after him would have perished.

CURRICULUM VITAE

Samuel Lee Kountz

October 20, 1930 - 1981

PERSONAL

Born:	Lexa, Arkansas

EDUCATION

1952	Arkansas AM and N, Pine Bluff, B.S.
1956	University of Arkansas Graduate School, Department of Chemistry, Fayetteville, M.S.
1958	University of Arkansas School of Medicine, Little Rock, M.D.

POSITIONS

1958-59	Intern, Stanford Service, San Francisco Hospital, San Francisco
1959-62	Assistant Resident, Department of Surgery, Stanford University School of Medicine
1962-63	Bank of America Giannini Fellowship, Stanford University School of Medicine and Postgraduate Medical School, Hammersmith Hospital, London
1963-64	Senior Resident, Department of Surgery, Stanford University School of Medicine
1964-65	Chief Resident, Department of Surgery, Stanford University School of Medicine
1965-66	Instructor, Department of Surgery, Stanford University School of Medicine
1965-66	Visiting Fulbright Professor to United Arab Republic (three months)
1966-67	Assistant Professor, Department of Surgery, Stanford University School of Medicine
1967-72	Associate Professor, Department of Surgery, University of California School of Medicine, San Francisco
1972	Professor, Department of Surgery, University of California School of Medicine, San Francisco
1972-81	Professor and Chairman, Department of Surgery, State University of New York Downstate Medical Center, Brooklyn

ORGAN PRESERVATION: A PERSONAL PERSPECTIVE

Folkert O. Belzer

Address: Department of Surgery
Clinical Science Center
600 Highland Avenue
Madison, Wisconsin 53792

Folkert O. Belzer

1990

1967

ORGAN PRESERVATION: A PERSONAL PERSPECTIVE

Folkert O. Belzer

Early Experience in Kidney Transplantation

My interest and involvement in organ transplantation and preservation started in San Francisco in 1966. I had been working in England in 1965, and when I returned to San Francisco, Dr. J. Englebert Dunphy, the Chairman of the Department of Surgery at the University of California, San Francisco, suggested that I work with John Najarian, M.D. Najarian had started a kidney transplant program about two years earlier and in that time, had performed approximately 40 kidney transplants in San Francisco, all from living-related donors. My task was to develop a cadaver kidney transplant program to supplement that program. At that time, the first heart transplant had not yet been performed, and brain death had not been clinically accepted by either the medical profession or the public.

Cadaver kidneys were typically removed after cardiac arrest and, therefore, always experienced a period of warm ischemia. Little was known about how warm (or even cold) ischemia affected the viability of the human kidney. It was known, however, that the longer the blood supply was severed from an organ, the greater was the likelihood of organ injury and loss of viability. Thus, we attempted, as much as possible, to limit the time between removal of the cadaveric kidney and its transplantation. The first few cadaveric kidney transplants performed by John Najarian and me were done by a method similar to that used for hepatic transplantation prior to 1987. I would start the donor operation after cardiac arrest and remove one kidney. If this kidney appeared to be transplantable, a call was made to Najarian at Moffitt Hospital, and he would start the recipient operation. The kidney would be rushed from the donor hospital - usually in San Francisco - to the University Hospital, where it would be transplanted immediately, limiting the ischemic time as much as possible.

Although the effects of these kidney transplants were dramatic and cadavers could be used as a source for organs, it was obvious that a better method of kidney transplantation was necessary. Specifically, we needed an improved method of preserving the organs so that higher quality kidneys could be obtained and there would not be such an emergency created by the procedure. Thus, I turned my attention to the laboratory to work on this problem.

Beginning Kidney Preservation

I had been in the laboratory with Bob Hoffmann and Glenn Downes, studying hepatic blood flow. The urgent need for an effective method to preserve the kidney forced us to abandon our studies and switch to studying hypothermic perfusion of the kidney. In a previous study, I had shown that continuous perfusion with whole blood was possible only for a short period of time and resulted in an increase in perfusion pressure within one-half hour of perfusion (1). Thus, we switched our attention to the use of plasma as a perfusate. With plasma, the perfusion pressure rise was delayed, but still occurred after about six to 10 hours, and no kidney was viable in the dog after 24 hours of perfusion. By incorporating a membrane oxygenator into the perfusion system and using a pulsatile pump, the rising perfusion pressure could be delayed further, but consistent viability was never obtained.

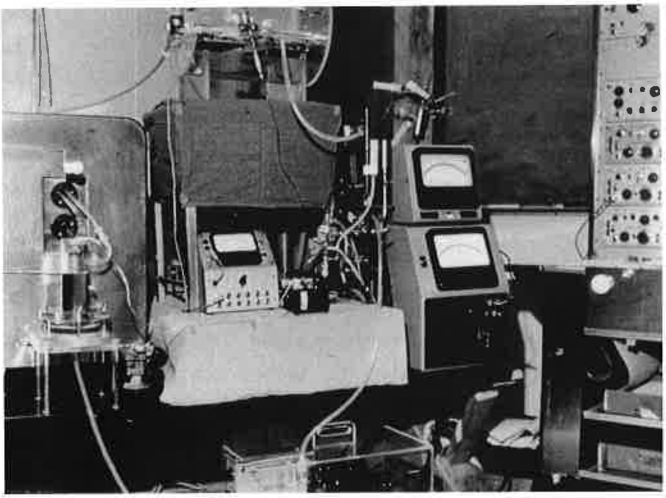


Figure 1. The perfusion circuit used for dog kidney preservation as well as the first human kidney. The membrane oxyengator is on the left, the pulsatile perfusion pump on the bottom, and the organ chamber on top. ca. 1967

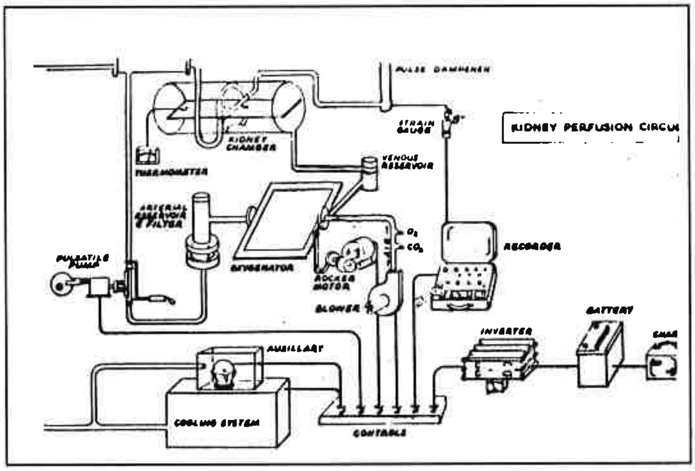


Figure 2. Schematic drawing of the perfusion circuit in the laboratory as well as the first transportable unit. ca. 1967

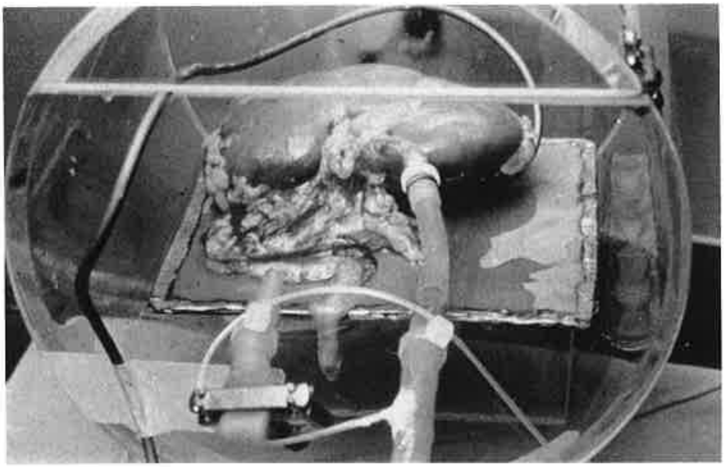


Figure 3. The first preserved and subsequently transplanted human kidney. August 1967

Although the success generated in any experimental laboratory depends upon inspiration and perspiration, it also helps to have some luck. We had always collected plasma from donor dogs and kept it frozen. The frozen plasma was taken from the freezer and allowed to thaw out overnight prior to the experiment. One morning, I arrived at the laboratory and found that the plasma had not been removed from the freezer the night before. Rather than postpone the experiment, we thawed the plasma rather rapidly by running it under hot water. To our surprise, the plasma was very turbid, quite unlike that we had previously used which had been thawed slowly. To obtain a clear solution, we filtered the plasma. The dog kidneys perfused with this plasma did not show a rise in perfusion pressure, and the kidneys functioned well after 24 hours of preservation and autotransplantation.

Subsequent studies showed that freezing and rapid thawing had produced coalescence of unstable lipoproteins in the plasma, which were then removed by the filtration (2). In the earlier experiments, these microaggregates of unstable lipoproteins had become trapped in the kidney's capillary system, especially in the glomerulus, and produced the rising perfusion pressure. This factor in unsuccessful hypothermic perfusion preservation of the kidney had now been eliminated. We named the new solution "cryoprecipitated plasma (CPP)" and used it to preserve dog kidneys for up to 72 hours with 100 percent survival after autotransplantation (3). This method of preservation was now ready to be tested in the clinical situation.

In August 1967, a middle-aged man with amyloidosis presented with renal failure, but because of his systemic disease, he had not been considered suitable for dialysis or for kidney transplantation. I had just harvested a kidney, which was placed on the preservation circuit in the laboratory (Figs. 1,2). I worked alone in San Francisco at this time; Najarian had left for Minnesota, and Dr. Sam Kountz would not arrive until several months later. I discussed the option to accept this kidney with the patient; he accepted. The transplant was performed with a total preservation time of 17 hours. The kidney (Fig. 3) functioned immediately, although not perfectly, and hypothermic perfusion preservation of a human kidney had become a reality (4). We were still unsure of human kidney tolerance to hypothermic preservation and, consequently, wanted to begin perfusion preservation immediately after harvesting the kidney in the donor hospital. However, we did not have a machine that was sufficiently portable to carry to the donor hospital. An unattended laundry cart was found in the hospital corridor one night and was immediately requisitioned for use in our laboratory. With the expertise of Chester Truman from the instrument shop at Moffitt Hospital, the laboratory perfusion equipment was modified to fit onto this cart. It was a wonderful machine to behold because everything moved. The membrane oxygenator, one of the first built by the Waters Company, consisted of a silastic envelope in which the fluid was oxygenated. This moved with a rocking motion. The pulsatile pump, organ chamber, and arterial and venous reservoirs were all made in the laboratory but functioned surprisingly well. It took two or three people to move the machine, and with a rented Avis truck and a forklift we were able to travel to any hospital in the vicinity (Fig. 4).

The first few times we used this perfusion machine, one of our procurement technicians, Ken Steeper, would drive the truck, while Bob Hoffmann and I sat in the back, supporting and steadying the perfusion machine with our feet. Subsequently, we decided to secure the machine with ropes tied to the truck, which was a fortunate idea. On one of the trips we had to stop suddenly to avoid an accident. The ropes held the machine, but the force of the

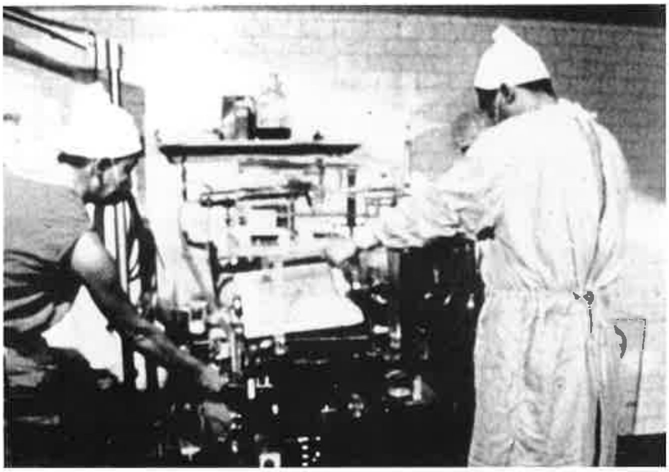
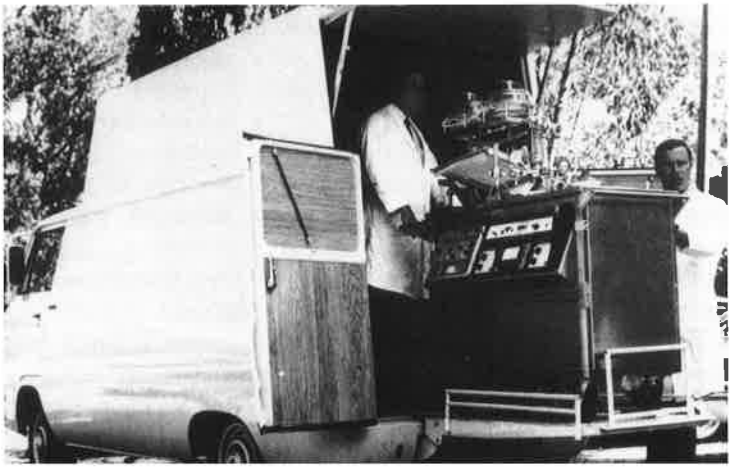


Figure 4. The transportable preservation unit in the operating room at San Francisco General Hospital attended by Ken Steeper on the left and Bob Hoffmann on the right. ca. 1968

Figure 5. The preservation van and machine with Bob Hoffmann and Ken Steeper. ca. 1969



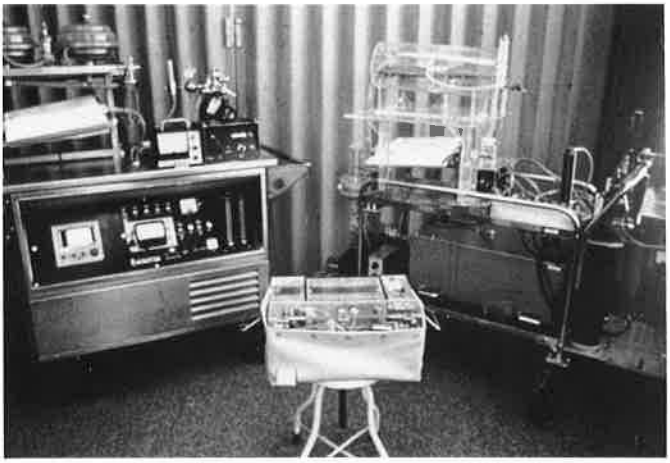


Figure 6. Progression of the perfusion equipment, the original homemade unit is in the right rear, the first commercially built unit left rear, and the homemade portable unit in front. ca. 1971

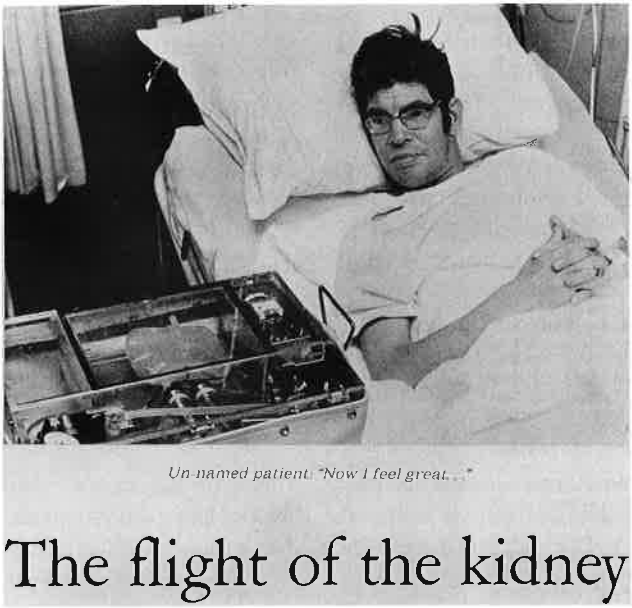
stop caused the steel frame of the perfusion cart to bend. Had this happened on one of our previous runs, Bob and I would undoubtedly have been crushed by the machine!

The first human kidney preserved by pulsatile perfusion worked after transplantation, but subsequent transplants were not as successful. Postoperative function in more than half of the first 30 kidneys preserved by pulsatile perfusion was poor or resulted in a nonfunctioning graft (5). These kidneys, unlike living-related kidney transplants, were obtained from less-than-ideal donors (ie, nonheart-beating cadavers). We noticed that these kidneys had very low flow rates during hypothermic perfusion. To study this problem we returned to the laboratory and reproduced the clinical situation of the agonal period, including warm ischemia, in the dog. The dog model was inconclusive, but we demonstrated the development of severe agonal vasospasm in the pig kidney preservation model, not only in the renal artery but also in the intrarenal vessels.

We found that this agonal vasospasm could be eliminated by performing a bilateral adrenalectomy one week prior to the donor operation. Thus, the cause of this problem appeared related to the release of catecholamines during the agonal period. We also found that pretreatment of the donor with adrenergic blocking agents such as regitine or dibenzyline (a better agent because it is long acting) completely abolished the agonal vasospasm (5,6). Pretreatment of all donors with dibenzyline was now introduced into our clinical procurement program resulting in dramatic improvement in the immediate function of the transplanted kidney. Cadaveric kidney transplantation ceased to be an emergency procedure at our hospital, where all cadaveric kidney transplants were performed electively during daytime hours (7).

Other improvements that contributed to simplifying organ harvesting occurred during this same period. The first commercial preservation unit was manufactured by American Hospital Supply. The Avis truck used to transport the machine was upgraded to a custom built van donated to the transplant service by our patients. It was a marked improvement and facilitated transport of this large machine (Fig. 5) with a lift bed to raise the machine in and out of the van and an electric generator to provide electricity. Bob Hoffmann, Ken Steeper, Sam Kountz, Dr. Oscar Salvatierra, and I traveled over 30,000 miles procuring kidneys. There was one nuisance. We were prone to receiving parking tickets whenever we parked the van near the emergency room of the donor hospitals because it looked like a laundry truck. I do not remember which one of us had the brilliant idea to add a red emergency light to the top of the van. We never used the light, and I do not believe that it even worked, but it provided us with a universal parking permit for any location.

Although the preservation machine was large, it was amazingly reliable and was used clinically until 1974. The preservation machine was miniaturized with the help of Chester Truman to obtain a truly portable unit (Fig. 6). This mini-preservation machine was tested extensively in the laboratory and was ready for a clinical trial; the opportunity arose over Christmas in 1971. We had harvested two type-A kidneys, but only one had a suitable recipient at that time. I called my good friend, Hans Dicke, a transplant surgeon in Leiden, The Netherlands, and found that they had a suitable recipient for the remaining kidney. I took the next flight from San Francisco to New York and transferred to the night flight to Amsterdam. I obtained a first class ticket to be sure to have sufficient room for the portable machine. It was Christmas Eve and the first class compartment in the 747 jet was empty except for one other passenger. Thus, I had the undivided attention of five stewardesses who kept bringing ice to keep the kidney cold. I vividly remember



Un-named patient: "Now I feel great..."

The flight of the kidney

Figure 7. The Dutch transplant recipient, the day after surgery with the portable perfusion circuit, the first successful transoceanic organ sharing. December 1971

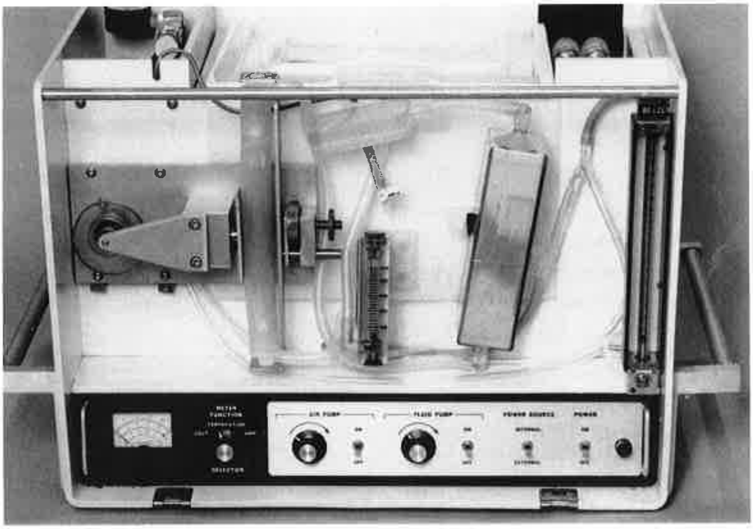


Figure 8. The commercially produced Mini-Belzer unit. ca. 1972
This unit, but without the flow meter, oxygenator, and CO2 valve, is still used by us today for clinical kidney preservation.

the Captain coming down to view the kidney and the preservation unit. He remarked how amazingly science had progressed. Here we were, flying at 30,000 feet at over 600 miles per hour in a remarkable and complex airplane, and here was a little homemade plastic box carrying, indeed, a very precious cargo. After 37 hours of preservation the kidney was successfully transplanted in a 42-year-old truck driver with polycystic kidney disease (Fig. 7). This was Leiden's 84th kidney transplant, and the transplant team included Drs. Dicke, Johan Terpstra, Maurits Kalff and Leo van de Putte. The recipient apparently returned to a normal lifestyle with excellent kidney function until he died 17 years later from a ruptured Berry aneurysm. The portable machine was subsequently produced commercially by Edwards Laboratory in California for several years as the Mini-Belzer unit (Fig. 8) and with some simplification is still used today for clinical kidney preservation at the University of Wisconsin.

A seminal paper was published in 1969 by Geoffrey Collins, M.D., working in Dr. Paul Terasaki's laboratory (8). In this study, dog kidneys were successfully preserved for 30 hours by simple cold storage after vascular flushout with a solution containing a high concentration of potassium and glucose. These kidneys regained immediate function following autotransplantation. Because of the simplicity of this method, it was rapidly adopted by many clinical transplant centers throughout the world. For the next two decades, very little was added to clinical preservation. Most studies that appeared during that period attempted to credit or discredit both preservation methods.

During this same time the concept of tissue typing emerged as important in kidney transplantation; some believed in this concept, while others did not. Thus, this controversy was further fueled by the fact that simple cold storage would allow easier sharing of kidneys between transplant centers on the basis of tissue typing. Because sharing of kidneys was simpler by cold storage than by continuous perfusion, cold storage became a more popular method. Actually, one of the reasons that our group developed long storage periods for the kidney was to allow sufficient time for tissue matching and sharing of the organ. Sam Kountz was a strong believer in the value of tissue typing for matching kidneys with recipients. I had become disillusioned with the value of tissue typing because in our own, rather large series of cadaver kidney transplants we could not show a beneficial effect of tissue typing for long-term graft survival (9). However, our interest in preservation by perfusion continued because immediate function of the kidney after transplantation was better with this method of preservation than with simple cold storage (10). We continue to use this method clinically for kidney preservation.

In the late 1960s and early 1970s, we attempted to use the same method of preservation developed for the kidney for two other organs - liver and heart. Our interest in liver preservation was stimulated by three clinical liver transplants performed by Dr. Alfred DeLormer and me in the early 1970s. While working in our laboratory, Dr. Donald Trunkey did a large number of experiments with dog heart transplants, none of which was successful. Dr. Robert May, Bob Hoffmann, and I did more than 120 porcine liver transplants without achieving consistently successful survival after 24-hour preservation (11). Because clinical liver transplant results were also quite dismal at that time, we decided to abandon further attempts to preserve the liver or heart.

Successful perfusion preservation of the kidney stimulated another area of clinical interest for me. In 1968, two young women were admitted to the University of California at San Francisco Hospital because of severe hypertension secondary to bilateral fibromuscular dysplasia of the renal arteries extending into the branch arteries.

This condition was considered inoperable at that time, and both patients underwent unilateral nephrectomy of the more severely involved kidney with subsequent discharge from the hospital, still hypertensive and with only half of their renal reserve.

Once again we took this problem to the experimental laboratory and in dog kidneys, showed that the branch vessels could be reconstructed using ex vivo hypothermic perfusion and microvascular repair (12). In February 1972, a 38-year-old woman was admitted to University Hospital with uncontrollable hypertension secondary to advanced bilateral fibromuscular dysplasia of both renal arteries with extension into the branch arteries. We operated on her in two stages, undertaking left nephrectomy ex vivo, renal artery repair, and autotransplantation with subsequent similar repair on the right side. After her surgery she become normotensive with normal renal function (13). The first autotransplant of the kidney had been performed in 1962 by Dr. Hardy for a ureteral injury (14), and the first autotransplant for renal artery disease was performed by Woodruff in 1965 (14,15); credit for the first ex vivo repair of the renal artery for renal vascular hypertension should go to Dr. Ota and his colleagues (16). This young woman, however, was the first patient in North America to be treated successfully by this combined method. We subsequently performed a larger clinical series of ex vivo renal repairs, again with good results (17). Although fibromuscular dysplasia can now usually be successfully treated by balloon dilatation, an occasional patient will still benefit from this surgical technique.

Move to Wisconsin

I moved to Madison in 1974, having accepted the Chairmanship of the Department of Surgery at the University of Wisconsin. In so doing, I made two excellent decisions and two mistakes. The two excellent decisions were to persuade Bob Hoffmann to join me in Wisconsin and to recruit James Southard, Ph.D., to work in my laboratory. The two mistakes were to forget to ask what my salary was and to find out the location of my laboratory space. The laboratory allocated to me was very small and poorly designed, but it had the advantage of being located across from the only large animal operating room (Fig. 9). Despite the inade-

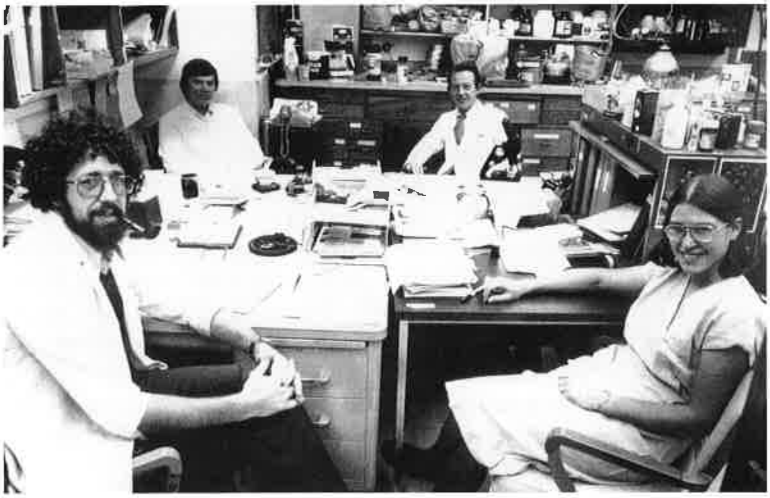


Figure 9. The preservation laboratory at the University of Wisconsin. In front, Jim Southard and our technician, Karen Senzig, in the back, Bob Hoffmann and the author. ca. 1975.

quate space, our laboratory became quite productive. I mention this only to remind junior investigators in surgery that, very often, the amount of laboratory space is not directly related to one's productivity.

In 1974, the clinical requirements for successful kidney preservation were relatively well met by either simple cold storage or continuous machine perfusion. We had not yet developed an interest in liver, pancreas, or heart preservation because the clinical transplantation of these organs was still very difficult and long-term success rates were not very good. Thus, we turned our research attention to understanding problems in organ preservation, specifically related to basic mechanisms of hypothermic-induced cellular injury and methods to prevent the injury.

Research is often based on serendipity, rather than solely on a detailed systematic mechanistic approach to a problem. There is nothing wrong with serendipity, and it often leads to successes. For instance, both advances in organ preservation–continuous perfusion and simple cold storage–had an element of serendipity. The development of cryoprecipitated plasma was aided by serendipity. Furthermore, Collins' discovery of an appropriate cold storage solution had a serendipitous element. Collins attempted to mimic the intracellular environment of the kidney and designed a high-potassium solution based on a report by Keeler (18). He ended up with a solution of only 170 mOsm/l, which was hypotonic to the kidney cells. He made the solution isotonic by the addition of a large concentration of glucose (about 130 mM); the addition of this impermeant was one of the main reasons for the success of this solution. Our laboratory was one of the first to show that the effectiveness of Collins' solution was due to the high concentration of glucose, rather than the cations or anions (19). Thus, potassium and sodium could be interchanged without losing the beneficial effects on the kidney, as long as either glucose or sucrose were added to the solution.

Although serendipity continues to be an important aspect of our research in organ preservation, there is no doubt that a more systematic approach could also lead to improving organ preservation. Thus, we began a more deliberate and basic consideration of how to develop improved organ preservation methods. Our goal was then, as now, to obtain truly long-term kidney preservation - weeks to months, rather than hours or days. To achieve truly long-term preservation may require cryopreservation (freezing) of the organ, an area in which we were not interested. Another possibility, however, is continuous perfusion, and we continued to experiment with this method of organ preservation. We continued to focus on the canine kidney and expanded to use models other than transplantation, including tissue slices, cell homogenates, isolated mitochondria, isolated perfused organs, and isolated cellular preparations.

The laboratory worked very hard, but results were slow to develop. Initially, we realized that endothelial cell injury appeared to limit long-term kidney preservation, and every kidney transplanted after five-day preservation turned black on reperfusion, signaling organ failure. We felt that this could be due to the unsatisfactory nature of the colloid necessary for oncotic support during continuous perfusion. Serum albumin was the commonly used colloid, but many laboratories had reported that different batches of albumin were better than others; this suggested that some factor related to albumin may have been causing endothelial injury. To test this, we used a common kitchen blender to whip the perfusate for a short time to accentuate its exposure to air. After only 24-hour preservation with this perfusate, the kidney was injured and most kidneys turned black on reperfusion. This simple experiment demonstrated to us that denaturation of albumin could lead to the formation of elements toxic to the endothelium of the kidney. Thus, we began a search for a stable, nontoxic, oncotic agent. We tried many compounds, including gums, dextrans, cross-linked hemoglobin, and albumin, all without success. Finally we found a compound, hydroxyethyl starch (American Critical Care, now DuPont Pharmaceuticals), that gave excellent three-day kidney preservation. The kidneys, however, still turned dark on reperfusion after five days of preservation. The starch was then subjected to an ultrafiltration-dialysis procedure to reduce the concentration of low molecular weight components (below 50 kilo daltons); this purified starch allowed preservation of the kidney for up to seven days without signs of endothelial injury, and all kidneys remained red on reperfusion although they did not function.

Next we turned our attention to the development of a purely synthetic perfusate for the kidney to take advantage of the beneficial properties of starch as a colloid. Previous albumin-containing perfusates were made in a sodium chloride-based solution, plasma, or Ringer's lactate. We were aware for many years that cells became edematous when stored in the cold, and we looked at the suppression of hypothermic-induced cell swelling. We knew what type of compound was desired - a larger molecular weight anion - but did not know which ones would be nontoxic, readily available, and inexpensive. We scanned the *Merck Index* looking for agents that would be effective in preventing cell swelling and searched the Sigma catalog to determine if these were available and relatively inexpensive. We found two compounds, gluconic acid and lactobionic acid - both acid forms of saccharides, glucose, and lactose.

It was in 1979 that we finally formulated what we thought was the ideal perfusate; it contained many agents that had a theoretical rationale for protecting the kidney from injury. This solution was called the 'kitchen sink' perfusate because it contained everything but the kitchen sink (Table 1). This solution contained all the ingredients that eventually became the University of Wisconsin (UW) solution, now used widely for organ preservation. However, the UW solution did not guarantee successful kidney preservation. A modified version containing gluconate was developed for human kidney perfusion preservation in 1984. It provided safe, three-day preservation of the kidney and replaced cryoprecipitated plasma. Thus, we had developed a purely synthetic perfusate for our clinical use (20).

Table 1. KSP ingredients.

Experiment #272	Date: 3/12/79
KSP - Kitchen Sink Perfusate	
Compound	Concentration
Lactobionic acid	80 mM
Succinic acid	5 mM
MgOH	10 mM
KH_2PO_4	10 mM
Caprylic acid	3 mM
Adenosine	10 mM
Glutathione	1 mM
Carnithine	2 mM
Butylated hydroxy anisole	0.1 mM
Butylated hydroxy toluene	0.1 mM
Propyl gallate	0.1 mM
$CaCl_2$	1.5 mM
Vitamin (MEM)	
Amino acids (essential MEM)	
Amino acids (nonessential MEM)	
Choline CL	30 mM
Raffinose	15 mM
Human serum albumin	3.75g%
Sodium hydroxide	

Potassium hydroxide to pH 7.4 at room temp
Final Values: Sodium=25 mM;
Potassium=65 mM; OSM=300 mOsm/l

Development of UW Solution

Several changes occurred in the early 1980s, both clinically and in research. First, we moved into the new medical center (Clinical Science Center), which provided more and better laboratory and experimental surgery space. Also, Hans Sollinger, M.D., joined the faculty after finishing his surgical residency at our institution and soon started a clinical pancreas transplant program. Munci Kalayoglu, M.D., who spent two years with Thomas Starzl, M.D., at the University of Pittsburgh, was recruited in 1984 as a pediatric surgeon as well as head of our liver transplant program. Another major change was the introduction of immunosuppressive agents at our center - cyclosporine in 1983 and OKT3 therapy in 1985. The availability of these two agents made pancreas and liver transplantation feasible.

Liver and pancreas transplantations were performed on an emergency basis, usually at night, and it was obvious again that there was a great need for successful preservation of these organs for longer than 24 hours. The success of perfusion for preservation of the kidney and our past experience with perfusion preservation led our group to initiate studies in the perfusion preservation of these two organs. Anthony D'Alessandro, M.D., worked in our laboratory as part of his resident training and had some impressive successes with 24- and 72-hour preservation of the dog liver as tested by orthotopic transplantation. However, this method was cumbersome and the results were inconsistent. Perfusion of the pancreas was also difficult because of its double arterial supply; this organ quickly became edematous during perfusion. Thus, we felt that the development of a method to successfully preserve these organs was going to be difficult and time consuming.

In 1985, Jan Wahlberg, M.D. from Uppsala, Sweden, joined our laboratory as a research fellow and was given the task of preserving the pancreas. We were aware that islet cell functions in the pancreas were relatively resistant to cold ischemia and that there was no need to preserve exocrine function. Therefore, we began to investigate simple cold storage. The first solution tested was similar to the 'kitchen sink' perfusate minus the additives that supported aerobic metabolism. To our amazement, this simplified solution, subsequently called the UW solution, was quite effective and provided consistent 72-hour preservation of the canine pancreas. These results were presented at the American Society of Transplant Surgeons in June 1986 where it attracted little interest (21). During the same month, three other research fellows joined our laboratory: Neville Jamieson, M.D., from Cambridge, England; Ralf Sundberg, M.D., from Lund, Sweden; and Rutger Ploeg, M.D., from Leiden, The Netherlands. Ploeg showed that the solution used by Wahlberg was effective for three-day preservation of the canine kidney by simple cold storage, but produced inferior renal function when compared to continuous perfusion (22).

Jamieson and Sundberg took over the liver preservation project and initially continued perfusion preservation as begun by D'Alessandro. However, because of the complexities of this method and the fact that relatively short-term preservation of the liver was required for clinical applicability (about 24 to 30 hours), it was felt that simple cold storage might be the method that would satisfy our goals most rapidly. Again, using the same solution as used by Wahlberg, our laboratory showed that livers could be preserved for 24 and 48 hours as tested in the orthotopic liver allograft model (23,24).

These were most encouraging results, and the next step was to introduce this solution into clinical liver and pancreas preservation. Clinical pancreas preservation with the UW solution was begun in 1987. Initially, pancreases were preserved for only short periods, but gradually the length of preservation was extended to up to 30 hours with excellent results. In the summer of 1987, we used the UW solution for clinical liver preservation. We still kept the preservation time under six hours, and the operations were still performed as emergency surgery. Because the transplantation of a poorly preserved liver could be a life-threatening situation for the recipient, we were very cautious about extending the preservation time.

However, an interesting and unpredictable situation presented itself that summer. We had procured a pediatric liver for a child with biliary atresia, but while the procurement team was harvesting the liver, the child was admitted for emergency surgery and found to be HIV positive. His distraught parents took the child home. Subsequently, the child was found to be HIV negative and was successfully transplanted several weeks later. We attempted to send the unused liver to another institution, but there was a concern that the preservation time was too long. The liver was in the cooler in the UW solution, and I thought that this would be a good opportunity to test the effects of a long-term preservation of the liver by performing a xenotransplant into a baboon. The next morning an adult baboon was obtained from another investigator at the University, and a successful xenograft was performed after 20 hours' preservation of the liver. The baboon's liver functions were near normal the day following surgery, but, unfortunately, the animal died 36 hours postsurgery from an anaphylactic reaction against infused human platelets. This experiment showed that the human liver was tolerant to up to 20 hours' cold storage in the UW solution and gave us confidence that we could extend our current clinical limit of about six hours to longer times.

Soon after this episode, a patient with end-stage liver disease was transferred from the intensive care unit of one of our referring hospitals to our intensive care unit. A liver became available in Texas, and because the recipient required a number of diagnostic procedures, the transplant was scheduled for 8:00 AM the next morning. The liver was successfully transplanted after 20 hours of preservation (Fig. 10); the recipient was extubated the next day and transferred to the transplant unit on the

Figure 10. The first "elective" liver transplant after 20 hours of preservation. August 1987

second postoperative day with excellent liver functions. He is alive and well today. Elective and scheduled liver transplantation became a reality and we continue to perform this operation on a scheduled basis unless the recipient's condition requires an emergency liver transplantation (25). It is interesting that this first elective liver transplant occurred exactly 20 years after the first successful elective kidney transplant.

The results of liver and pancreas preservation with the UW solution were first presented at the International Transplant Congress in Pittsburgh honoring Tom Starzl for his pioneering work in organ transplantation. We presented our experimental results along with some of the clinical results, and the attendees at the Congress seemed to be impressed. I think the attention was greatest, however, when I presented two slides: one showing Starzl sleeping in a Lear jet and the other showing me sleeping at home in my own bed. These slides illustrated the benefits, at least to the surgeon, of having an available method for preserving the liver for 24 hours or more. No longer would it be necessary for all livers to be harvested and immediately transplanted, regardless of the hour.

Our experience with the UW solution in clinical liver and pancreas transplantation was soon tested at other centers and its efficacy confirmed. Although the UW solution has received most of its attention from liver preservation, its effect on pancreas preservation and transplantation is, in my opinion, just as significant. At our center, it has almost completely eliminated vascular thrombosis, postoperative graft pancreatitis, and primary nonfunction (26).

Our preservation laboratory continues to work on the basic mechanisms of organ injury during hypothermic storage. One of our next goals is successful preservation of the heart. Long-term organ storage remains nearly as elusive as it was 20 years ago, but we have made some progress in clinical organ preservation for transplantation of the intraabdominal organs. In the future, we hope to have similar success in the preservation of intrathoracic organs.

Experimental organ preservation in the laboratory and the clinical application of our results has been an important and very gratifying part of my academic and professional life over the past 25 years. I am especially grateful to my colleagues, Jim Southard, Bob Hoffmann, the late Glenn Downes, and the many technicians, residents, and research fellows who contributed enormously to our modest successes. Table 2 lists the surgeons from overseas who contributed to our efforts and were a major force in what has been accomplished. My transplant colleagues, Hans Sollinger, Munci Kalayoglu, John Pirsch, and Tony D'-Alessandro, as well as our transplant fellows, have been enthusiastic and major contributors to our results. I am also very grateful to the National Institutes of Health for their uninterrupted support for the past 25 years.

Table 2. Research fellows from overseas.

Research Fellows		
B.S. Ashby - England	J.T. Williams - England	H. Pienaar - South Africa
R.E. May - England	R.W.G. Johnson - England	T. van Gulik - The Netherlands
J.P. Pryor - England	J.R. Wahlberg - Sweden	K. Boudjema - France
T.V. Keaveny - Ireland	R.J. Ploeg - The Netherlands	M. Schilling - Germany
D.F. Scott - Australia	N.J. Jamieson - England	B. den Butter - The Netherlands
D.R. Martin - Australia	R. Sundberg - Sweden	A. Saunders - Australia
F.O. Stevens - Australia	K. Claesson - Sweden	S. Lopukhin - Russia

Preservation is only a small part of the overall picture in transplantation. Many hands, heads, and hearts are necessary for such successful undertakings. I have been fortunate to have been joined by many fine professionals. Without the excellent skills of a highly competent and dedicated staff of transplant surgeons, physicians, organ procurement personnel, nurses, and others, it would have been much more difficult to show how organ preservation is effective in the clinical situation. When I look back over the past years, I must admit that, as a clinician, my satisfaction has come from surgery and the care of the surgical patient. As an academician, my satisfaction has come from teaching medical students, especially surgical residents and transplant fellows. The laboratory, however, has been the most stimulating to my intellect, both when things went well and when there was little progress. The experimental laboratory provides an opportunity to be creative and to make discoveries that can improve the quality of life for our patients.

REFERENCES

1. Belzer FO, Park HY, Vetto RM. Factors influencing renal blood flow during isolated perfusion. Surg Forum 1964; 15:222.
2. Belzer FO, Ashby BS, Huang JS, et al. Etiology of rising perfusion pressure in isolated organ perfusion. Ann Surg 1968; 168:382.
3. Belzer FO, Ashby BS, Dunphy JE. 24-hour and 72-hour preservation of canine kidneys. Lancet 1967; 2:536.
4. Belzer FO, Ashby BS, Gulyassy PF, et al. Successful 17-hour preservation and transplantation of human-cadaver kidney. N Engl J Med 1968; 278:608.
5. Belzer FO, Reed TW, Pryor JP, et al. Cause of renal injury in kidneys obtained from cadaver donors. Surg Gynecol Obstet 1970; 130:467.
6. Keaveny TV, Pryor JP, White C, et al. Renal vasomotor responses in the agonal period. Angiology 1971; 22:77.
7. Belzer FO, Kountz SL. Preservation and transplantation of human cadaver kidneys: A two-year experience. Ann Surg 1970; 172:394.
8. Collins GM, Bravo-Shugarman M, Terasaki PI. Kidney preservation for transportation. Initial perfusion and 30 hours' ice storage. Lancet 1969; 2:1219.
9. Belzer FO, Perkins HA, Fortmann JL, et al. Is HLA typing of clinical significance in cadaver renal transplantation? Lancet 1974; 1:774.
10. Belzer FO. Preservation of cadaver kidneys: Cold storage or machine perfusion. Arch Surg - Ed 1983.
11. Perkins HA, May RE, Belzer FO. Cause of abnormal bleeding after transplantation of pig liver stored by a perfusion technique. Arch Surg 1970; 101:62.
12. Belzer FO, Keaveny TV, Reed TW, et al. A new method of renal artery reconstruction. Surgery 1970; 68:619.
13. Belzer FO, Salvatierra O, Perloff D, et al. Surgical correction of advanced fibromuscular dysplasia of the renal arteries. Surgery 1974; 75:31.
14. Hardy JD. High ureteral injury: Management by autotransplantation of the kidney. JAMA 1963; 184:97.
15. Woodruff MFA, Doig A, Donalds KW, et al. Renal autotransplantation. Lancet 1966; 1:433.
16. Ota K, Mori S, Awane Y, et al. Ex situ repair of renal artery for renal vascular hypertension. Arch Surg 1967; 94:270.

17. Belzer FO, Salvatierra O, Palubinskas MD, et al. Ex vivo renal artery reconstruction. Ann Surg 1975; 182:456.

18. Keeler R, Swinney J, Taylor RMR, et al. Br J Urol 1966; 38:653.

19. Downes GL, Hoffmann RM, Huang JS, et al. Mechanism of action of washout solutions for kidney preservation. Transplantation 1973; 16:46.

20. Hoffmann RM, Southard JH, Lutz M, et al. 72 hour preservation of dog kidneys using a purely synthetic perfusate containing hydroxyethyl starch. Arch Surg 1983; 118:919.

21. Wahlberg JA, Love R, Landegaard L, et al. 72 hour preservation of the canine pancreas. Transplantation 1987; 43(1):5.

22. Ploeg RJ, Goossens D, Vreugdenhil P, et al. Successful 72 hour cold storage kidney preservation with UW solution. Transplant Proc 1988; 20:935.

23. Jamieson NJ, Sundberg R, Lindell S, et al. Successful 24-30 hour preservation of the canine liver. Transplant Proc 1988; 20(1):945.

24. Jamieson NV, Sundberg R, Lindell S, et al. Preservation of the canine liver for 24-48 hours using simple cold storage with UW solution. Transplantation 1988; 46(4):517.

25. Kalayoglu M, Sollinger HW, D'Alessandro AM, et al. Successful extended preservation of the liver for clinical transplantation. Lancet 1988; 1:617.

26. Sollinger HW, Stratta RJ, D'Alessandro AM, et al. Experience with simultaneous pancreas-kidney transplantation. Ann Surg 1988; 208(4):475.

CURRICULUM VITAE

Folkert O. Belzer

PERSONAL

Born:	October 5, 1930, Soerabaja, Indonesia
Marital Status:	Married, 4 Children
Home Address:	6105 South Highlands Avenue Madison, Wisconsin 53705
Office Address:	Department of Surgery Clinical Science Center 600 Highland Avenue Madison, Wisconsin 53792

EDUCATION

1951-53	Colby College, Waterville, Maine, (Chemisty) B.A.
1953-54	Boston University, Boston, Massachusetts, (Biology) M.A.
1954-58	Boston University School of Medicine, M.D.
1958-59	Internship Grace-New Haven Hospital, New Haven, Connecticut
1959-62	Assistant Resident, Grace-New Haven Hospital
1962-63	Chief Resident, University of Oregon Medical School

BOARD CERTIFICATION

1964	American Board of Surgery

POSITIONS

1963-64	Instructor in Surgery, University of Oregon Medical School
1964-65	Senior Lecturer, Guy's Hospital, London, England
1966-69	Assistant Professor of Surgery, UCSF Medical Center
1969-72	Associate Professor of Surgery; Co-Chief, Transplant Service, UCSF
1972-74	Professor of Surgery; Chief, Transplant Service, UCSF
1973-74	Director, Experimental Surgery Laboratories
1974	University of Wisconsin Head, Section of Transplantation Chairman Division of General Surgery Professor of Surgery Chairman, Department of Surgery

PROFESSIONAL SOCIETIES

American College of Surgeons

American Medical Association

American Society of Transplant Surgeons
    1975 President

American Surgical Association

Central Surgical Association

Halsted Society
Pacific Coast Surgical Society
Society for Vascular Surgery
Society of University Surgeons
Transplantation Society
Western Surgical Association
Southern Surgical Society
Royal Netherlands Academy of Arts and Sciences

EDITORIAL BOARDS AND EDITORSHIPS

Transplantation
Transplantation Proceedings, Clinical

PUBLICATIONS

Total: 420

A PERSONAL MEMORY OF ANTILYMPHOCYTE SERUM AND ITS IMPACT ON TRANSPLANTATION

Anthony P. Monaco

Address: Harvard Medical School
New England Deaconess Hospital
185 Pilgrim Road
Boston, Massachusetts 02215

Anthony P. Monaco

Teaching medical students in Boston, 1967.

1990

A PERSONAL MEMORY OF ANTILYMPHOCYTE SERUM AND ITS IMPACT ON TRANSPLANTATION

Anthony P. Monaco

As I begin to write this recollection of the early days in the development of antilymphocyte serum, two things are immediately apparent. First, it is my 59th birthday! A lot of time has passed since those heady days when the first truly effective experimental biological immunosuppressive agent was demonstrated. Second, and perhaps more important, personal memories of scientific events should not be subjected to the same rigorous evaluation as an experiment accepted for a peer-reviewed journal. The memoirist will no doubt tend to dwell on his own (and those of their colleagues') contributions. Such a natural tendency is the essence of a personal memoir; it should not, however, be construed as a deliberate attempt to minimize the important work of others.

My own interest in immunology, transplantation, and antibodies started early. I was a student at Harvard Medical School (1952 to 1956) when future Nobel prize winner Joseph Murray and his colleagues electrified the medical world with their first successful kidney transplant between identical twins. Organ transplantation is so commonplace today that it is hard for those who were not around then to comprehend the impact of this event. I certainly wanted to be a part of this exciting and embryonic field. I also vividly recall the second year immunology lectures given by Byron Waksman, then a very young assistant professor, and Albert Coons, who was first beginning his work with fluoresceinated antibodies to immunochemically identify antigen and antibody in histological sections to study the process of antibody formation. Everything is so far advanced now that we tend not to realize how little we knew of immunology and allograft rejection at that time. Indeed Albert Coons' studies proved that plasma cells were the final cells involved in antibody formation. I trace my interest in immunological research to the early influence of these two men and I trace my interest and enthusiasm for the field of transplantation to Joe Murray and his team.

After graduation from medical school, I was fortunate to have my surgical training at the Massachusetts General Hospital (MGH) under Dr. Edward D. Churchill. Dr. Churchill's concept for the training of an academic surgeon emphasized that future surgical researchers should be trained in science in a basic science (nonsurgical) research laboratory. He felt a good academic surgeon with such training could eventually establish his own laboratory in a department of surgery and, hopefully, do quality research which might attract young scientists

Graduation from Harvard Medical School in 1956.

(non-MDs) to work with him. Although this was a revolutionary idea at the time, his idea was prescient for the field of transplantation. Nowadays, basic scientists working in clinical transplantation departments and laboratories as equal partners (and vice versa) with clinical transplanters are commonplace. The same is obviously true for other areas of basic science and clinical activity. The important thing for me was that my surgical mentor reinforced my desire to integrate basic science and clinical work.

In 1960, I took time out from my surgical residency to do a year of basic science at Harvard Medical School with Al Coons who was then at the height of his fame; he seemed to be receiving a prize every month for his pathfinding studies in the use of fluorescent-tagged antibody to study antibody formation. Although he was a frequent candidate for the Nobel Prize, this honor eluded him. Billingham, Brent, and Medawar had done their famous experiments on actively acquired tolerance to skin allografts achieved by neonatal injection of replicating donor lymphoid cells (1). Classical immunologists were studying tolerance to defined soluble antigens induced in normal adult animals by chronic antigen injection. Albert Coons and I hoped to induce tolerance to defined proteins in mice (as demonstrated by lack of serum antibody production) and then see if antibody could be demonstrated histologically on cells. The assumption being tested was that animals might be making antibody which was being "mopped-up" by excess antigen (identifying antigen-antibody complexes in those days was fairly rudimentary). Also, we hoped to identify the presence of antigen (or a fragment thereof) in a "tolerant cell." We used an impure form of bovine serum albumin (BSA) to induce tolerance in adult mice with chronic administration of BSA. No antibody was found in serum or histological sections. After a year of hard work, we submitted the paper to the *Journal of Experimental Medicine*. The paper was eventually rejected because after its submission (several months after I left the laboratory to return to my residency) a very purified form of BSA became available. The reviewers felt that ours was a good experiment but it should be repeated with the highly purified BSA which would render interpretation of the data more significant. Unfortunately, I had left the laboratory and was in surgery at the MGH, up every other night on-call, with no time for laboratory work so this could not be done. Although we never published this work, I have always felt the scientific training I had with Al Coons was one of the best learning experiences I ever had. He was a scrupulously honest person of immense personal and scientific integrity. I was fortunate to be exposed to him at a time early in my research career.

A special highlight of my year with Dr. Coons was my first meeting with Peter Medawar. He had not yet received the Nobel Prize when he was invited to give Harvard's Dunham Lectures and to visit the immunological laboratories. All faculty members, graduate students, and research fellows were given appointments with this already very famous man for varying lengths of time proportionate to their faculty rank, scientific experience, and esteem and general all-round importance in the department. As the newest and youngest research fellow in the department (and a surgeon to boot) of dubious immunological potential, I was given the last few minutes of Medawar's time on his last day. As luck would have it, everyone ahead of me went overtime; after my appointed time had been passed by several hours, I assumed that he would just forget about me. I recall leaving the laboratory and going across the Harvard Quadrangle to lunch at the student dining room at Vanderbilt Hall. Shortly thereafter, a running, short-of-breath Hugh McDevitt (then a research fellow for two years studying with Dr. Coons) came to tell me that Professor Medawar was "waiting for me!" I ran back to the laboratory to find Medawar sitting on his suitcase beside my bench waiting to discharge his final "obligation" as the visiting Dunham Lecturer. We had a brief but enlightening talk about adult tolerance to soluble protein antigens, and then they whisked him away to the airport. Needless to say, I was struck by the dignity and courtesy which this extraordinary man showed to a very young and inexperienced research fellow. We were to meet many times again in the future.

After completing my residency in 1963, I had the good fortune to stay on at the MGH as an associate of Paul Russell to start the clinical transplantation program there and to work in the transplantation laboratory. One of our first projects was to review the literature (both experimental and clinical) of the field of transplantation. This culminated in the publication of the Biology of Tissue Transplantation (2). Perhaps the best estimate of how small our knowledge of transplantation was at that time was that the entire field could easily be encompassed in a series of review articles! In the laboratory, I had the great good fortune and personal pleasure to meet Mary Wood and initiate a life-long scientific association and personal friendship. My first laboratory project extended the interest of my studies with Albert Coons by focusing on attempts to isolate murine cell-free transplantation antigens from the spleen which were capable of sensitizing an allogeneic recipient to spleen donor strain tissues (3). This could easily be done from the spleen but not from the liver. Indeed, incubation of identical murine cell-free antigenic preparations from the spleen and liver destroyed the sensitizing potency of splenic extracts to subsequent specific skin grafts (4), a phenomenon we never explained adequately, although we postulated there was a factor in liver that somehow altered potent splenic transplantation antigens. In view of the recent observations that combined transplantation of the liver with other organs (especially the small bowel) seems to protect the nonhepatic organ from rejection, we probably should return to this area of study. Incidentally, extensive studies to infuse various forms of cell-free extracts to induce tolerance in adults gave only very modest results at best (5).

Antilymphocyte serum (ALS) soon became the focus of the laboratory. As I recall, my first interest in ALS was a more or less spontaneous idea. As with a lot of laboratory work, I was unaware of the previous work by many others [Metchnikoff, Besredka, Christian and Leen, Pappenheimer, Cruickshank, Waksman, J. Sachs, etc. (6-12)]. I was not even aware of the work of Woodruff and colleagues (13,14) initially. In association with Ian Gray, then a research fellow in the laboratory, we immunized rabbits with mouse lymphocytes and systematically studied the in vivo and in vitro effects on the immune response of the rabbit antimouse lymphocyte serum (RAMLS). Prior to ALS, prolongation of skin allografts across the mouse H-2 locus with any degree of success was a rarity. Woodruff had prolonged rat allografts well with ALS combined with thoracic duct drainage. The mouse ALS was extraordinarily effective; not only were primary allografts prolonged across the H-2 but

With the first mouse rendered tolerant with ALS in 1966.

secondary skin allografts and even rat xenografts enjoyed prolonged survival. These studies, and those of others, sparked an enormous, worldwide interest in antilymphocyte serum to ameliorate allograft rejection. The lasting impression I have of these early days of ALS research was that of excitement and exhilaration. We felt that ALS had been identified in the past but our new work clearly focused on and demonstrated its extraordinary potential for experimental transplantation studies and possible clinical application. There were so many things to study with ALS I felt we just could not do the experiments fast enough.

The classic study by J.F.A.P. Miller (15) had demonstrated the importance of neonatal thymectomy on immune development. However, demonstration of the importance of the adult thymus to immune integrity and recovery was not easily achieved. Claman and colleagues (16) had shown that mice that were totally irradiated and "rescued" with autologous (syngeneic) bone marrow did not recover immune function as well if they were thymectomized as adults. The importance of the integrity of the adult thymus gland to recover after peripheral ablation of the immune system was clearly demonstrated in our report (17) that adult thymectomized animals recovered from the tissue and peripheral lymphopenia and depression of immune responses induced by ALS much more slowly than normal, ALS-treated animals. It is noteworthy that shortly thereafter, Jeejeebhoy (18) confirmed that ALS was an extremely potent immunosuppressive agent in adult thymectomized animals. These studies with ALS and adult thymectomy are very important, even today. As we attempt to induce allograft tolerance in immunologically competent adult animals using polyclonal and monoclonal antibodies, the necessity for thymic ablation in induction of peripheral tolerance in adult animals is becoming more apparent. Also, these studies with adult thymectomy and ALS showed how useful ALS could be just as an experimental reagent in the design and execution of immunological studies.

The next obvious question to be asked of ALS was whether its extraordinary effectiveness could be reproduced in large animal species with whole organ immediately-vascularized grafts. At this time, Richard Simmons joined our laboratory and he participated in our first experiments utilizing a horse anticanine lymph node lymphocyte serum to prolong the survival of canine renal allografts. As I review these studies, I feel they were extraordinary for the times (19,20). Of seven dogs treated with various protocols of equine RALS, only one sustained a normal rejection; all others enjoyed varying degrees of prolonged survival and two survived over 350 days with essentially normal histology. Shortly thereafter, Tom Starzl and others used a horse anticanine ALS with similar impressive results.

With the wonderful results we obtained in dogs and the extraordinary results we had just obtained to induce tolerance and chimerism in adult-thymectomized, ALS-treated mice across the H-2 locus (see below), we were really flying high and it just seemed that we could accomplish everything we asked of ALS. It was natural that human testing of ALS efficacy should be done. As best I can determine, the first demonstration of the immunosuppressive effect of ALS was achieved by our group and reported later at a special conference on ALS held in California and later published (21). Looking back at these early trials strongly suggests that if presented with the same opportunity today, we certainly could not have done them as we did. Antihuman lymphocyte serum was prepared by immunization of rabbits with cadaveric lymph node lymphocytes incorporated into Freund's adjuvant followed a month later by an intravenous booster injection of saline-suspended lymphocytes (as we had done for mice). A 7S gamma globulin fraction of the crude rabbit ALS was prepared using ammonium sulfate precipitation and DEAE cellulose fractionation. The material had excellent lymphoagglutinin activity against lymph node cells and washed peripheral blood lymphocytes and it had surprisingly little human hemagglutinin activity in vitro.

The next question was how should this potential immunosuppressive agent be tested and on whom. As best I can recall, there was no institutional review board review for this kind of research at that time. We selected a few subjects to be treated with a brief course of rabbit antihuman lymphocyte 7S gamma globulin followed by tests of immune competence. The interesting subject selection included one patient with chronic lymphatic leukemia (he might benefit by lysis of his excessive population of pathological lymphocytes) and four uremic patients maintained on hemodialysis (they might benefit from demonstrated immunosuppression with ALS for their future transplant). Most amazing, as I look back, is that for five healthy "volunteers" we used the wives of patients who had been transplanted or were awaiting a transplant. We were reassured that they would best comprehend the importance of this experiment (they were the best according to the doctrine of "informed consent" - a doctrine that had not yet been formally elaborated). Nowadays, I think most of us would be reluctant to use family of patients waiting for transplants since requests for participation in a related experiment might be considered a form of subconscious coercion.

Subjects received 5-10 cc of gamma globulin deep s.c. on days 1, 3, and 5 followed by delayed skin testing and multiple skin allografting. We found all the things later shown with large-scale ALS testing in humans. Local reactions at the injection sites were quite painful and there was the usual febrile response. Peripheral lymphopenia (down to 10 percent of preinjection levels) occurred rapidly after the first injection, but unfortunately our leukemic patient had no change in his peripheral lymphocyte burden. Existing preinjection-positive delayed sensitivity skin reactions were clearly rendered negative by the ALS treatment for varying periods of time (up to two to six weeks after cessation of therapy) even after blood lymphocyte counts had returned to preinjection levels. Skin allografts from various donors were placed on the five ALS-treated volunteers. We determined that their survival was prolonged (12 to 19 days) as compared to the survival of a control group of 39 skin allografts (8 to 13 days) done in another group of healthy volunteers as part of a tissue typing study done by Ian Gray and Paul Russell. We identified antihuman rabbit globulin antibodies in several of the patients and even one bout of mild clinical serum sickness (they were not on any steroids or other immunosuppression as ALG-treated transplant patients would eventually be treated). Most importantly, the normal patients who received the 7S antilymphocyte gamma globulin showed no evidence of impaired renal function or damage six months after the administration of 7S-RAHLS. We concluded that small amounts of 7S-RAHLS are indeed immunosuppressive in man and that the results, though obviously modest, were clearly encouraging. Later, Najarian and colleagues (22) did a really effective study of their Minnesota ALS on skin allograft rejection in multiple sclerosis patients given varying doses per kilogram of body weight of the material. Although no effect was found on the course of the disease, skin allografts enjoyed prolonged survival in relation to the dose of ALS given. Their study definitely showed that human ALG was immunosuppressive versus the human allograft reaction. At the same time, Tom Starzl and his colleagues were beginning to use an equine antihuman lymphocyte globulin preparation extensively along with additional immunosuppressive therapy in patients receiving renal allografts. Here, too, the ALG-treated patients were thought to have done "better" when compared with previous control patients; unfortunately, failure to perform concurrent controls would plague human ATG trials for many years to follow.

By January 1967, the interest and enthusiasm for ALS research was so active that a special study group meeting on antilymphocyte serum was held in London at the Ciba House under the auspices of the Ciba Foundation. Researchers from the active ALS groups were invited and memories of this meeting are among my fondest ones about the early days of transplantation. It was a small meeting with only 24 attendees; just six papers - each given about an hour for presentation and discussion - comprised the agenda. As a young researcher, it was a real thrill to present and then participate in detailed discussions with such luminaries as Peter Medawar, John Humphrey, James Gowans, Michael Woodruff, and Dirk van Bekkum. Medawar (and his colleagues Eugene Lance, Ray Levey, and Robert Taub) did outstanding work on ALS. Indeed, Medawar told me he found the period of ALS research one of the most exciting and fruitful times in his research career. Also, I came to know well (essentially for the first time) a very young Roy Calne, Richard Batchelor, Hans Balner, and Tom Starzl.

The meeting resulted in the speedy publication of a small volume (23) with the six long papers and a detailed discussion of each. As I review this today, it is amazing how well the discussion identified the future problems and prospects of ALG therapy. Currently, transplantation is such a big, active multidisciplinary field that even "small" meetings have large attendance with plenary and poster sessions, etc. I wonder if we members of the transplant community should try to develop a vehicle for small, focused deliberations. When the meeting was ended, everyone was eager to return to his laboratory to investigate the wealth of experimental and clinical possibilities of ALG. I remember Medawar's parting comment to me at the reception at his house following the meeting. He obviously felt my enthusiasm on being welcomed into the transplant community as he remarked, "Well Tony, you have joined the club now. Just remember that we have one requirement for membership in this club: don't solve the problem of transplant rejection and spoil it for all of us!" Peter Medawar, more than anyone else, enjoyed the opportunity to meet and discuss science with his friends and admirers.

One of the most exciting areas of ALS investigation was its use in inducing tolerance. To me, the profound tissue and peripheral lymphopenia induced by ALS and adult thymectomy seemed to mimic the physiological state of the neonatal animal with its transient state of physiological immunosuppression. Infusion of appropriate numbers of replicating lymphoid cells (as was done by Medawar and colleagues in their classic *Nature* paper (1) on acquired immunological tolerance) during this time therefore seemed an ideal way to induce tolerance in the adult animal and thereby reproduce Medawar's experiment done in neonates. Injection of F1 hybrid lymphoid cells into ALS-treated adult-thymectomized recipients induced unequivocal donor-specific tolerance. This state was accompanied by long-lasting chimerism and the tolerance could be broken by infusion of normal recipient lymphoid cells or recipient cells sensitized to the donor. Thus, all the parameters of acquired immunological tolerance of Billingham, Brent, and Medawar were reproduced in this study. I presented these findings at the Transplantation Meeting in New York in February 1966 (actually before our meeting at the Ciba House). I had not seen Medawar since my research fellow days with Albert Coons but I picked him out sitting right up front. To my dismay, there was a great deal of difficulty with the projector so that our beautiful data (at least I thought it was so) was never real-

(Left to right) Robert Taub, Anthony Monaco, Peter Medawar, and Michael Woodruff at the Ciba Meeting on ALS in 1967.

(Left to right) Paul Russell, Ray Levey, Richard Batchelor, and Anthony Monaco at the Ciba Meeting on ALS in 1967.

(Clockwise) Anthony Monaco, John Merrill, Francis Moore, Joe Murray, William Curran, John Mannick, and Paul Russell at the establishment of the Boston Interhospital Organ Bank (which later became the New England Organ Bank and Region I of UNOS) in 1969.

Jim Gowans leading a panel on ALS at the Second International Transplantation Congress.

ly properly presented. I did see Medawar's frustration during the presentation - he suffered fools badly whether they were speakers or projectionists. The proceedings of the meeting were published in the *Annals of the New York Academy of Science* (24) with a publication date of December 1966, but the actual volume did not come out until many months later.

In 1969, I left the MGH to set up an entirely new transplantation laboratory and clinical service at Harvard and Boston City Hospital. Very quickly I became busy, productive, and happy with work at the new laboratory and unit. Mary Wood, who also had left the MGH, joined me at the new laboratory after a year with Dirk van Bekkum in Rijswick. We were also joined by a young surgical resident, Mark Hardy, who was my first research and clinical transplantation fellow. Shortly thereafter, Jim Gozzo joined the laboratory as a postdoctoral fellow to start what has been over two decades of fruitful collaboration and the closest friendship. Jim Gozzo developed several variations of ALS in vitro assays (rosette incubation) and purification (hemagglutination columns) still in use today. We were also focused on experimental tolerance systems with ALS. Levey and Medawar had used F1 lymphoid cells after ALS treatment without adult thymectomy to obtain a significant degree of tolerance. F1 hybrid lymphoid cells were an experimental artifact which would never be available clinically. We tried to substitute nonreplicating cells (hepatic, epidermal, renal, etc.) with no success. Eventually, very low doses of lymphoid cells (non-F1 hybrid) were carefully tested and bone marrow cells clearly were found to be an optimal cellular antigen for tolerance induction after ALS treatment (25-27). This bone marrow ALS model has occupied much of our research for a long time and we were joined in it by Takashi Maki who did much to analyze the cellular suppressor mechanisms involved in this form of tolerance including the identification of a donor-derived veto cell as part of the suppressor mechanism. Needless to say, it has been a source of great personal satisfaction that the model has been repeatedly verified by others and easily applicable to large animals as our own initial studies in dogs and the later studies in monkeys of Judy Thomas have shown. Although our first attempts in man to demonstrate the salutory effect of ALS and bone marrow in human cadaveric renal transplantation were only suggestive in identifying the efficacy of bone marrow (28), the recent work of Barber and colleagues (29) clearly has shown that donor-specific bone marrow infusion improves graft survival, reduces the requirement for immunosuppression and is associated with a microchimeric state which we identified in mice almost 20 years ago (30,31). There is no doubt in my mind that our current methods of nonspecific immune suppression will continue to improve as new drugs - FK506, rapamycin, newer monoclonal antibodies, etc. - become available. I also believe that the new immunosuppressive agents will be used to facilitate tolerance and unresponsiveness, most likely in association with polyclonal ALS and/or various monoclonal antibodies and in conjunction with additional donor-specific antigen. Our work these past many years strongly suggests that the optimal cellular antigen for this will be donor-specific bone marrow.

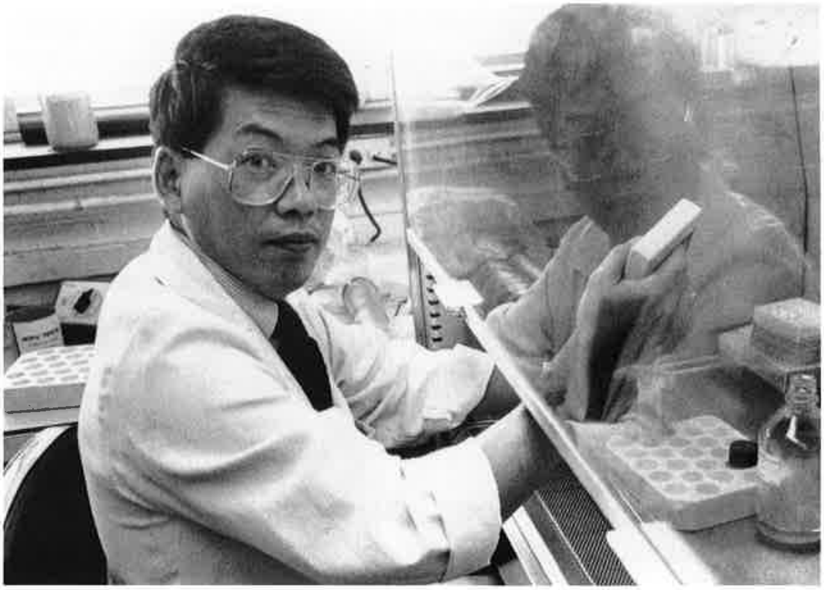
The early years of experimental and clinical work with ALS taught us a great deal which became relevant in all areas of transplantation. One of the milestones of early ALS history was the ALG therapy and standardization workshop held at Bad Soden under the auspices of the Behring Institute (32). Representatives from laboratories all over the world working on ALG were in attendance. It was here that I first met the late Professor Walter Brendel from Munich, an early pioneer in ALG development, and several of his many stu-

Mary Wood monitoring the suppression of the donor/recipient immune response through a lymphocyte count.

Mark Hardy at the Boston City Hospital, 1969

James Gozzo and Mary Wood , 1970

(Left to right) Anthony Monaco, Mary Wood, and Calvin Stiller



Takashi Maki, M.D., Ph.D., setting up a mixed lymphocyte culture at the Research Transplantation Lab in 1984.

dents who were destined to become leaders in transplantation such as Rudolf Pichlmayr and Walter Land. I think this excellent meeting was the first transplant symposium of the type now sponsored by The Transplantation Society and published in *Transplantation Proceedings*. Every aspect of experimental and clinical work being done on ALG at that time was considered and the problems at hand were identified. Although the clinical results were still inconclusive, the fact that so many groups had suggestions for improvement and evidence of clinical efficacy gave great impetus to continued investigation of ALG. A second important aspect of this meeting was that it foreshadowed the significant role the biotechnology industry would play in the future development of new immunosuppressive agents.

The early days of ALG clinical testing also taught us a lot, especially about how not to test a new immunosuppressive agent. The first commercial ALG in the United States, ATGam (Upjohn Co.), was tested as an adjunctive prophylactic, immunosuppressive reagent for cadaveric kidney transplantation. Multiple centers were utilized in this trial, some with very little clinical transplant experience and all with varied immunosuppressive protocols into which ALG was to be incorporated. The large number of centers was supposed to even out all the variables. Also, the studies took place at a time when our detailed knowledge of clinical transplantation was developing (we were just becoming aware of the transfusion effect!) so there was no stratification for important variables and risk factors in the ALG-versus-non-ALG groups. No wonder statistically significant differences were hard to come by. Eventually, adequate improvement with ALG therapy provided enough support for licensing and commercial availability. With the latter, ALG could be tested at limited, large centers and careful studies could be done to show its excellent effectiveness in the treatment of rejection, the delay and attenuation of rejection, the protective effect of ALG in the ATN kidney, etc. Indeed, as we test new monoclonal antibodies for efficacy our early studies with ALG have taught us to limit the questions asked and to stratify the risk factors in both groups.

In summary, ALG or ALS has had a significant impact on transplantation. First, ALS is a widely accepted experimental biological reagent that can be used for induction of transient immunosuppression. Its wide experimental acceptance can best be realized by the fact that immunobiological studies which depend heavily on ALS methodology in experimental execution have titles that do not contain the word ALS. Secondly, ALS was the first demonstrated effective biological immunosuppressive reagent in man and probably continues to be the most effective one. Thirdly, we need transient peripheral lymphoid ablation as we seek to induce peripheral or extrathymic tolerance in transplantation, and ALS may be the optimal means to do so. Studying and working on ALS has been fun, and it is not over yet.

Walter Brendel (left) and Leslie Brent in Kitzbuhl, 1988

(Left to right) Leslie Brent, Sir Roy Calne, Anthony Monaco, and Mary Lou Monaco in San Francisco, 1990

Anthony Monaco (second from left) with friends on Falaka Island, Kuwait, in 1990

Anthony Monaco (left) with Walter and Claudia Land at Axams, Austria, in 1990

REFERENCES

1. Billingham RE, Brent L, Medawar PB. Acquired immunological tolerance. Nature (London) 1953; 172:603.

2. Russell PS, Monaco AP. Biology of tissue transplantation. Little, Brown and Co., Boston, MA, 1965.

3. Monaco AP, Wood ML, Russell PS. A simple method for preparation of cell free transplantation antigens: physical and biological properties. Surg Forum 1964; 15:133.

4. Mandel MA, Monaco AP, Russell PS. Destruction of splenic transplantation antigens by a factor in the liver. J Immunol 1965; 95:673.

5. Abbott WM, Monaco AP, Russell PS. Antilymphocyte serum and cell free antigen loading. Transplantation 1969; 7:291.

6. Metchnikoff E. Etudes sur la resorption des cellules. Ann Inst Pasteur 1899; 13:737.

7. Bisredka A. La leucotoxine et son action sur le systeme leucocytaire. Ann Inst Pasteur 1900; 14:390.

8. Christian HA, Leen JP. Some further observations oon leucotoxins. Boston Med Surg J 1905; 152:397.

9. Pappenheimer AM. Experimental studies upon lymphocytes. II. The action of immune sera upon lymphocytes and small thymus cells. J Exp Med 1917; 26:163.

10. Cruikshank AH. Antilymphocyte serum. Brit J Exp Pathol 1941; 22:126.

11. Waksman BH, Arbouys S, Arnason BG. The use of specific "lymphocyte" antisera to inhibit "hypersensitive" reactions of the delayed type. J Exp Med 1961; 114:997.

12. Sachs JH, Fillipore DR, Hune DN. Studies of immune destruction of lymphoid tissue. I. Lymphocytotoxic effect of rabbit anti-rat lymphocyte serum. Transplantation 1964; 2:60.

13. Woodruff MFA, Forman B. Effect of antilymphocyte serum on suspensions of lymphocyte in vitro. Nature 1951; 168:35.

14. Woodruff MFA, Anderson N. Effect of lymphocyte depletion by thoracic duct fistula and administration of anti-lymphocyte serum on survival of skin homografts in rats. Nature 1963; 200:702.

15. Miller JFAP, Marshall AHE, White GR. Immunological significance of the thymus. Adv Immunol; 2:111.

16. Claman HN, Talmadge DW. Prolongation of immunological tolerance in the adult mouse. Science 1963; 141:1193.

17. Monaco AP, Wood ML, Russell PS. Effect of adult thymectomy on the recovery from immunological depression caused by antilymphocyte serum. Science 1965; 149:432.

18. Jeejeebhoy HF. Effects of rabbit anti-rat lymphocyte plasma on immune responses of rats thymectomized in adult life. Lancet 1965; 2:106.

19. Monaco AP, Abbott WM, Otherson HB, et al. Antisera to lymphocytes: prolonged survival of canine allografts. Science 1966; 153:1264.

20. Abbott WM, Monaco AP, Otherson HB, et al. Prolonged survival of renal allografts in dogs treated with antilymphocyte serum. Surg Forum 1966; 17:228.

21. Monaco AP, Wood ML, Russell PS. Some effects of purified anti-human lymphocyte serum in man. Transplantation 1967; 5:1106.

22. Najarian JS, Merkel FK, Moore GE, et al. Clinical application of lymphoblast serum. Transplant Proc 1969; 1:460.

23. Monaco AP, Wood ML, van der Werf BA, et al. Recent observations of antilymphocyte serum in mice, dogs, and man. Ciba Foun-

dation Society Group, No. 29, London, J & A Churchill Ltd., 1967; 111.

24. Monaco AP, Wood ML, Russell PS. Studies of heterologous antilymphocyte serum in man. III. Immunological tolerance and chimerism produced across the H-2 locus with adult thymectomy and antilymphocyte serum. Ann NY Acad Sci 1966; 129(1):190.

25. Gozzo JJ, Wood ML, Monaco AP. Use of allogeneic, homozygous bone marrow cells for the induction of specific immunologic tolerance in mice treated with antilymphocyte serum. Surg Forum 1970; 21:281.

26. Monaco AP, Wood ML. Studies on-heterologous antilymphocyte serum inmice. VII. Optimal cellular antigen for induction of tolerance with antilymphocyte serum. Transplant Proc 1970; 2:489.

27. Gozzo JJ, Wood ML, Monaco AP. Use of minimal doses lymphoid cells for production of heterologous antilymphocyte serum. Transplant Proc 1971; 3:779.

28. Monaco AP, Wood ML, Maki T, et al. Attempt to induce unresponsiveness to human renal allografts with antilymphocyte globulin and donor-specific bone marrow. Transplant Proc 1985; 17:1312.

29. Barber WH, Diethelm AG, Laskow DA, et al. Use of cryopreserved donor bone marrow in cadaver kidney allograft recipients. Transplantation 1989 47:66.

30. Monaco AP, Gozzo JJ, Wood ML, et al. Use of low doses of homoozygous allogeneic bone marrow cells to induce tolerance with antilymphocyte serum (ALS): Tolerance by intra-organ injection Transplant Proc 1971; 3:680.

31. Liegeois A, Escourrow J, Ouvre E, et al. Microchimreism: A state of low ratio proliferation of allogeneic bone marrow. Transplant Proc 1977; 9:272.

32. ALG Therapy and Standardization Workshop, Bad Soden, April 23-25, 1972, Behring, Institute Research Communication #52, Behringwerke AG, Marburg, 1972 (September).

CURRICULUM VITAE

Anthony P. Monaco

PERSONAL

Born:	March 12, 1932; Philadelphia, Pennsylvania
Address:	25 Farlow Road Newton, MA 02158

EDUCATION

1952	University of Pennsylvania, B.A.
1956	Harvard Medical School (Magna cum laude), M.D.

LICENSURE

1957	Massachusetts License Registration
1963	American Board of Surgery
1965	American Board of Thoracic Surgery

POSITIONS

1956-57	Surgical Intern, Massachusetts General Hospital
1957-58	Third Assistant Surgical Resident, Massachusetts General Hospital
1958-60	Second Assistant Surgical Resident, Massachusetts General Hospital
1960-61	Research Fellow in Immunology (with Dr. Albert H. Coons), Department of Bacteriology and Immunology, Harvard Medical School
1961-62	First Assistant Surgical Resident, Massachusetts General Hospital
1962-63	Chief Resident, West Surgical Service Massachusetts General Hospital
1962-63	American Cancer Society Clinical Fellow Massachusetts General Hospital
1962-63	Teaching Fellow in Surgery, Harvard Medical School
1963-66	Instructor in Surgery, Harvard Medical School
1963-66	Assistant in Surgery, Massachusetts General Hospital
1964-66	Tutor in Medical Science, Harvard Medical School
1966-67	Clinical Associate in Surgery, Harvard Medical School
1966-67	Assistant Surgeon, Massachusetts General Hospital
1967-69	Assistant Professor of Surgery, Harvard Medical School
1967-73	Associate Visiting Surgeon, Fifth (Harvard) Surgical Service Boston City Hospital
1967-73	Chief, Transplantation Division, Sears Surgical Research Laboratory of Harvard Medical School, Boston City Hospital
1968-	Active Staff Member, New England Deaconess Hospital
1969-77	Associate Professor of Surgery, Harvard Medical School

1972-74	Tutor in Surgical Science, Harvard Medical School		
1974-83	Member, Board of Academic Advisors, Harvard Medical School		
1974-	Courtesy Staff, Faulkner Hospital		
1974-	Associate Surgeon, Beth Israel Hospital		
1974-	Member, Cancer Research Institute, New England Deaconess Hospital		
1975-	Chief, Division of Organ Transplantation Deaconess-Harvard Surgical Service, New England Deaconess Hospital		
1977-80	Associate Scientific Director, Cancer Research Institute New England Deaconess Hospital		
1977-	Professor of Surgery, Harvard Medical School		
1980-	Scientific Director, Cancer Research Institute New England Deaconess Hospital		
1988-	President of Medical Staff, New England Deaconess Hospital		
1988-	Member, Board of Trustees, New England Deaconess Hospital		

PROFESSIONAL SOCIETIES AND COMMITTEES

	New England Organ Bank		
		1970-	Trustee
		1973-76	Chairman
		1981-85	Chairman
1978-81	Board of Directors, Kidney Foundation of Massachusetts		
	National Institutes of Health		
		1973-77	Member, Surgery A Study Section
		1981-	Special Reviewer, Immunobiology Study Section National Institutes of Health
		1983-	Member, Clinical Sciences Study Section,
1964-	New York Academy of Sciences		
1965-	Massachusetts Medical Society		
1965-	American Association for Advancement of Science		
1965-	American College of Surgeons, Massachusetts Chapter		
		1974-82	Member, Surgical Forum Committee
		1979-81	Councillor
		1981-	Chairman, Program and Education Committee
		1985-86	President
1965-	The Boston Surgical Society		
1966-	The Society of University Surgeons		
1966-	The Transplantation Society, Charter Member		
		1971-74	Treasurer
		1974-78	Secretary
		1978-80	Vice-President
		1986-88	President

1966-	The American Association of Immunologist
1966-	Reticuloendothelial Society
1966-	The Royal Society of Medicine
1966-	European Dialysis and Transplant Association
1970-	International Society of Lymphology
1970-	Surgical Biology Club
1971-	The Society for Surgery of the Alimentary Tract
1973-	American Surgical Association
1974-	New England Surgical Society
1974-	American Society of Transplant Surgeons, Charter Member
	1980-82 Councillor-at-Large
	1982-84 Treasurer
	1985-86 President
1975-76	Member, Advisory Committee, End-Stage Renal Disease, Bureau of Quality Assurance, Department of Health, Education and Welfare
1975-	The American Society of Nephrology
1975-	Italian Surgical Research Society, Correspondent Member
1977-80	Member, Merit Review Board in Immunology, Veterans Administration
1977-	Council of Biology Editors, Inc.
1978-	International Society of Surgery
1979-81	Member, Harvard Medical School Alumni Council
1980-	The Pancreas Club
1988-	The Transplantation Society of Australia and New Zealand (Honorary Member)

AWARDS

1951	Phi Beta Kappa
1952-56	National Scholar, Harvard Medical School
1955	Alpha Omega Alpha
1956	Henry Asbury Christian Award of Harvard Medical School
1968	Lederle Medical Faculty Award of Harvard University

EDITORIAL BOARDS

1969-	Transplantation (Editor)
1970-	Transplantation Proceedings (Editorial Board)

PUBLICATIONS

Total: 351

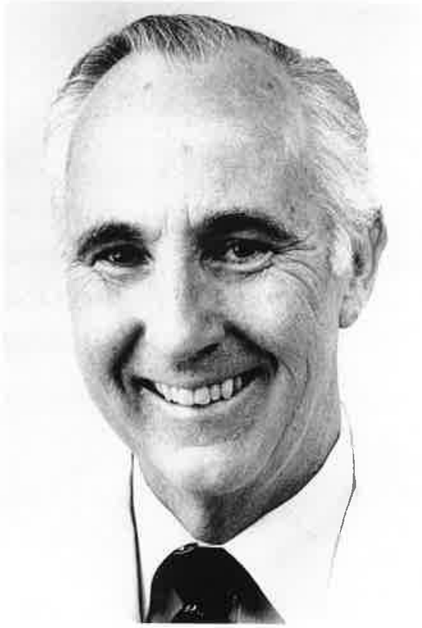
TRANSPLANTATION: PERSONAL RECOLLECTIONS

Peter J. Morris

Address: Nuffield Department of Surgery
University of Oxford
John Radcliffe Hospital
Headington, Oxford, OX3 9DU

Peter J. Morris

1961



1990

TRANSPLANTATION: PERSONAL RECOLLECTIONS

Peter J. Morris

I went to Medical School at the University of Melbourne from 1951 to 1957 and was blissfully unaware of any of the pioneering developments in transplantation that were occurring in the 1950s. During that time, David Hume had carried out cadaver transplants in Boston and Joe Murray had successfully performed the first identical twin transplant also in Boston, while Servelle, Dubost, and Kuss had performed renal transplants in Paris. Even our new Professor of Surgery at Melbourne, Maurice Ewing, had performed a cadaveric renal transplant in 1956 in Melbourne when I was in my penultimate year as a medical student, but I was quite unaware that this had happened! Our teaching in immunology as medical students was fairly rudimentary, it being really the immunology of microbiology. The total number of lectures on more basic immunology as we understand it today, as I recollect, was comprised of three lectures from Sir MacFarlane Burnet who was later to be awarded the Nobel Prize with Peter Medawar. I can remember that he lectured to us on the recognition of self and nonself which seemed entirely logical, though I did not realize what a revolutionary concept in thinking about the im- mune response this was proving to be, such was my general ignorance of immunology.

After I graduated at the end of 1957 I became a resident medical officer and surgical registrar at St. Vincent's hospital for the next three years, having decided even as a medical student that I wanted to be a surgeon. In those days there was no formal training in surgery in Australia and we mostly all took ourselves off to England to be further trained. Again, like most young surgeons heading overseas, I worked my passage as a ship's doctor on a cargo passenger boat, for which I was paid a shilling. My first post was as a Dominions Fellow at Guy's Hospital with Sir Hedley Atkins after which I became a resident surgical officer at The Royal Postgraduate Medical School at the Hammersmith Hospital with Professor Ian Aird.

This provided my first exposure to transplantation as the Hammersmith was one of the pioneer transplantation centers in Europe. It was here that Dempster had carried out his seminal work in kidney transplantation in the dog in the early 1950s, and where Ralph Shackman, the Professor of Urology, had introduced hemodialysis to the Hammersmith. Shackman, with Dempster, had begun a human renal transplant program some years before. In 1962, during my time at the Hammersmith, plans for a transplant between a living nonrelated donor and recipient were made. Both donor and recipient were doctors who were partners in general practice near Newbury in Berkshire. The patient with renal failure was Dr. Clark, and he was to receive a kidney from his partner, Dr. Spence. This was the first living-unrelated transplant to be performed in the world as far as I am aware. I was not immediately involved with the transplant procedure, but Alastair Smellie, a close friend and now a consultant surgeon at Cambridge, was the resident surgical officer working with Professor Shackman at the time. I well remember on the evening before the transplant operation he discovered that, despite the extensive investigations of the donor and recipient, some how or other the donor had not had a chest x-ray. He immediately got one done and to his horror there was a cavity in one lung, presumably tuberculous. He rang Professor Shackman to let him know about this transplant had gone too far to turn back and that the transplant would go ahead as planned!

The transplant did go ahead and was relatively uneventful. The donor was treated for tuberculosis postoperatively I believe and never turned a hair and was back in his practice a few weeks later. Indeed, a week after the operation Shackman and Dempster went on holiday leaving Alastair Smellie to mind the ship and keep in touch with them by phone!

The recipient had been immunosuppressed with total body irradiation and the kidney certainly functioned for a month or two, as I recollect, before the patient died of overwhelming infection. After his death the patients from his practice near Newbury decided to raise funds in his memory and so the Dr. Clark Memorial Fund for Transplantation was established, with the trustees of the fund based in Reading. By a strange turn of events, after I came to Oxford to the Chair of Surgery and established a transplant unit some 12 years later, the fund was still in existence. The trustees of the Dr. Clark Fund felt that it was appropriate as Reading and Newbury were in the Oxford region and would be served by the new Oxford transplant unit, that the fund be handed over to the University of Oxford to be administered by me as I thought appropriate. The Dr. Clark Memorial Fund for Transplantation continues to this day as a major source of funds for our research program in transplantation biology at Oxford and is the fund in particular that the patients, their families, and friends support.

However, returning to that time in 1962, I have to say that I was not particularly impressed with my first exposure to renal transplantation; in fact I am told that I was alleged to have said that I did not see too much future in clinical renal transplantation!

I then went to spend a splendid year at Southampton as a surgical registrar with Tom Rowntree before being lucky enough to be asked to join the surgical residency program at the Massachusetts General Hospital (MGH) in Boston through the efforts of Dr. Claude E. Welch. Paul Russell had just become Chief of Surgery and had begun renal transplantation at the MGH. During my year as a resident in 1964 I had the opportunity to see living-related renal transplantation performed and certainly the early results were most encouraging, bearing in mind that azathioprine had become available. Nevertheless, my interest in the area was somewhat marginal. At the beginning of 1965 I became a research fellow in Jack Burke's laboratory, my work involving the study of infection and inflammation. During that period I first made a rabbit anti-guinea pig lymphocyte globulin, not to study its effect on allograft rejection, but to study the immune response to staphylococcal infections in the guinea pig (1). I also became very interested in the capacity of free split-skin grafts, both syngeneic and allogeneic, to control infection and promote healing, this being relevant to the management of chronic ulcers and burn wounds (2).

Paul Russell's laboratory, which to a considerable extent was devoted to the definition of histocompatibility between donors and recipients of kidney transplants, was across the corridor from my laboratory, and so I became quite interested in this work, which of course was directed at the cellular determination of histocompatibility, eg, mixed lymphocyte reactions, normal lymphocyte transfer tests. The correlation between the outcome of living-related transplants and these cellular tests of histocompatibility was certainly promising. Many of the research fellows working with Paul Russell were from elsewhere, like myself, and we used to meet regularly and discuss our research efforts. These included Eddie Guiney, later to become Professor of Pediatric Surgery in Dublin, Sam Nelson who became Director of Histocompatibility in the Northern Ireland transplant unit, Gordon Johnson later to become Professor of Ophthalmology at the

University of London, and Ian Gray who became a Consultant Surgeon at Stoke-on-Trent in England, to name just a few of the Foreign Legion. All were working in transplant research and gradually I became more and more interested not only in transplantation but also in the area of histocompatibility.

This interest was further stimulated by Maurice Ewing, the Professor of Surgery in Melbourne, writing to say that their relatively new but very successful renal transplant unit needed to develop an interest in histocompatibility, and perhaps I should consider changing my research interests from infection to histocompatibility and transplantation. I remember going to chat with Paul Russell about this and he felt that the future of histocompatibility lay in serology and was rather doubtful whether, if that were to happen, a surgeon would be able to cope with the intricacies of serology! However he arranged for me to visit Bernard Amos at Duke University and Paul Terasaki at UCLA, and as well Jon van Rood was shortly to visit the MGH for a week or two in order to type their living-related donors and recipients. Thus, I had the opportunity of seeing three different approaches to the primitive serological definition of leukocyte antigens by three of the leaders in this area at the time. I decided that Paul Terasaki with his cytotoxic assay had the best approach to this, at least from a technical point of view, and made another visit to Terasaki's laboratory fairly soon after. Michel Jeannet from Geneva, now Professor of Immunology there, had also come to join Paul Russell and was establishing serological typing at the MGH, using the Amos technique, and we had many useful exchanges about the serological definition of leukocyte antigens in transplant patients and their donors.

At the end of 1966 I was due to go back to my new post at the University of Melbourne under Professor Maurice Ewing when the University there went through a financial crisis and my job was frozen. I remember Maurice Ewing phoning me not long before Christmas to give me the bad news and asking if it would be possible to stay on in Boston as he felt sure that he could get this job freed up in due course. Staying in Boston, Jack Burke assured me, was not a problem, but Mel Williams, who had been a resident with me at the MGH a couple of years earlier, had been out in Melbourne at the Walter and Eliza Hall Institute working with Gus Nossal and had just returned to David Hume's unit at the Medical College of Virginia (MCV) in Richmond. He had heard of my predicament from Melbourne and mentioned this to David Hume. And so just before Christmas I had a phone call from David Hume asking me whether I would be prepared to come down and set up a tissue typing laboratory in his department at MCV. As Hume had established the Medical College of Virginia as one of the major pioneer units in transplantation it seemed a golden opportunity, and so I accepted the offer with alacrity. When I arrived, not only had my old friend Mel Williams established an immunology research laboratory, but also not long after that Alastair Smellie, another old friend from Hammersmith days, arrived to work as a research fellow in Hume's unit.

I was in Richmond for not much longer than six months but I must say it was a marvelously productive and exciting six months. When I got there I found that there was a huge -80°C freezer stuffed with sera from before and after transplantation of every patient that Hume had transplanted, a total of over 100 patients, which of course at that time was a unique experience. Part of the deal with David Hume was that if I came to Richmond then I could spend as much time at UCLA with Paul Terasaki as I needed and, indeed, I must have gone back and forth to Los Angeles from Richmond at least three times during that six or seven months in Richmond, establishing a long-lasting friendship with Paul Terasaki. Hume's rationale for collecting this marvelous store of sera was that someday someone would know what to do with it, and indeed with this selection of sera I was able to demonstrate with Paul Terasaki for the first time in the human that cytotoxic antibodies directed against histocompatibility antigens were present in the sera of patients after transplantation and particularly after they had rejected a transplanted kidney (3,4). Also, it was possible to show that in the presence of cytotoxic antibodies against the donor, immediate rejection of the kidney would occur.

Indeed, I will never forget the one weekend when we saw three hyperacute rejections in four transplants. David Hume had been somewhere in South America as a visiting professor for several weeks and had just returned, desperately anxious to do some operating. During that weekend we had two donors and several recipients in whom I had demonstrated the presence of cytotoxic antibodies, and Hume was to do all four transplants. I was aware of course of Fleming Kissmeyer-Nielsen's paper on hyperacute rejection in the presence of a positive crossmatch using leukoagglutination and also Terasaki's suggestion a couple of years earlier that one patient who had cytotoxic antibodies directed against a donor had lost a kidney immediately. David Hume did not believe in the concept of hyperacute rejection not ever having seen a kidney fail immediately. I can remember his disbelief during the first transplant when after 20 minutes or so the kidney, which had perfused nicely and was putting out urine, started to go dusky and blue and shut down. Mel Williams took a biopsy from this kidney, raced off to the laboratory where he processed it as a frozen section, and came back and said that the kidney was stuffed with polymorphonuclear leukocytes and that this was an antibody-mediated destruction of the kidney. Meanwhile I had also continued working in the laboratory with the sera directed against donor lymphocytes and shown that they reacted with a titer of 1:16 with the donor. David Hume then said that he would leave the kidney in for two or three hours to see if the antibody would be removed, and if so, then use the other kidney from the same donor. After two or three hours I was able to show that the titer against the donor had dropped to one in two or thereabouts so Hume removed the first kidney, replaced it with the second kidney, and lo and behold the same thing happened again! The next day two more transplants were done and again another one underwent a classical hyperacute rejection in the presence of a positive crossmatch demonstrated later on the same day by myself. Numerous other tests were done on these patients which were later described with some other cases by Mel Williams, myself, and other colleagues in the *New England Journal of Medicine* in 1968 (5). Another key person in the transplant program at Richmond was H.M. Lee (recently President of the American Society of Transplant Surgeons) a young Korean surgeon whom David Hume had brought to Richmond. He had become David Hume's right hand man on the clinical front, being a superb technical and caring surgeon and was a person Hume felt quite happy leaving his patients to during his many absences.

David Hume was a fascinating person to work for and I suppose was a surgeon's surgeon. A charismatic person, he was one of the giants of those early days in transplantation, and it certainly was an experience to work with him in more ways than one. He lived on Coca Cola and had a dispensing machine installed outside his office so that bottles were available at all times. Segregation was just ending in the South, but at MCV the Black staff still stayed in their canteen and the White staff in theirs. Hume, who really did not eat lunch, made a habit of going to the Black dining room for lunch a couple of times a week, just to make a point. Quite rightly the flashing beacon on the top of MCV was known as the tower of David! Another foible of Hume's was his refusal ever to answer a letter, firmly believing that God made telephones to use and that there was no need for letters. This was somewhat of a problem when any of us wanted references, and I remember when I had returned to Melbourne needing a reference for an NHMRC grant. My professor (Maurice Ewing) had been tipped off that Hume hadn't replied to the request for a reference. Hume's secretary, well used to this problem, every day had been moving the request from the NHMRC onto the top of an ever-growing pile of correspondence which was never touched (or even read most of the time). Eventually she resolved the situation by getting Mel Williams to write the reference, after which Mel stuck it under his nose with the request "sign here, Chief," which was duly done and in due course the grant was awarded!

Towards the end of my time at Richmond before returning to Melbourne I took part in the Third Histocompatibility Workshop in Torino as part of the Terasaki team where for the first time the prototype of the microtray and the microcytotoxic technique were used. It was an exciting three weeks during which we all were studying some selected Italian families in order to define the inheritance of the leukocyte antigens, which were considered to be the major histocompatibility complex (MHC) in man. Ceppellini, who had organized the Workshop, kept everybody working ruthlessly from early morning to late in the day. I think we started work at 7:30 or 8:00 every morning. His only concession to that was to be on Sundays when he announced that for the Catholics among the participating groups he had arranged for Mass to be said in the laboratories at 7:30 AM and the rest could sleep in and start half an hour later! After the Workshop in the Torino laboratories we went for a three-day conference in the Italian Alps at Val D'Aosta where I presented my cytotoxic antibody data for the first time. This was followed immediately by the First Congress of the Transplantation Society in Paris, which was a marvelous meeting and enormously exciting for a young transplanter just to see and hear some of the giants in the field. I particularly remember the eloquence of Peter Medawar when he talked about tolerance. Mel Williams presented some work there that we had done on transplant recipients with the nephrotic syndrome, making a case for antibody in its etiology (6). I also first met Gus Nossal, not long appointed as the new Director of the Walter and Elisa Hall Institute in Melbourne in place of Sir MacFarlane Burnet. He provided enormous encouragement for me to return to Melbourne, as obviously I had some reservations about this, and Hume was offering me all sorts of inducements to stay at MCV. But who could resist a Nossal in full flight!

Towards the end of 1967 I returned to Melbourne to join Maurice Ewing's department at the University of Melbourne at the Royal Melbourne Hospital and to once again set up yet another histocompatibility laboratory, the first in Australia. The cadaveric renal transplant program started by Priscilla Kincaid-Smith and Vernon Marshall in 1963, had exceptionally good results once they started using azathioprine in 1964. Typing cadaveric donors in those days was a slow and tedious procedure and one was often working with backgrounds of close to 50 percent (as I had in Richmond). To start with, I used the old wax trays that Terasaki sent to get me started before the plastic trays became available. Nevertheless, in 1968 I was able to show the first correlation between cadaveric graft outcome and leukocyte typing (7). In those days there were often long nights for I would be involved not only in tissue typing the donor and recipient but also in the donor nephrectomy and subsequent renal transplant. No significant preservation of the kidney was possible at that time and the kidneys had to be removed after cessation

Italian Alps, 1967. Bernard Amos and Peter Morris turn back from Mont Blanc.

Australia's first tissue typing team at Royal Melbourne Hospital, 1968. (Left to right) Alan Ting, Peter Morris, John Stocker, and Wendy Law (front).

of cardiac activity. The tissue typing and crossmatching were done on peripheral blood from the donor. This was followed by the donor nephrectomy and then the transplant, all of these being performed continuously over about a 15-hour time span.

In 1968 I was asked to join a committee established by the Australian Government to plan a rational distribution of facilities and resources for dialysis and renal transplantation in Australia, a unique step for a government to take at that time (8). The committee was chaired by John Loewenthal, Professor of Surgery at Sydney University, a powerful medico-political figure in Australia. This committee eventually resulted in the establishment of an Australian and New Zealand system for the exchange of kidneys (Australplant) and the unique Dialysis and Transplant Registry. It was here that I first met Ross Sheil who had been a Rhodes Scholar and then a resident in surgery at Oxford and had recently returned to Sydney from a time as a research fellow with Joe Murray at the Peter Bent Brigham in Boston. He was to establish a fine transplant unit at the Royal Prince Alfred Hospital in Sydney and later became the first Professor of Transplantation in Australia at the University of Sydney and Director of the first Liver Transplant Program in Australia. He was also no mean tennis player, and over the years Roy Calne and I spent much effort trying to beat him on the courts, but to no avail.

I was interested in all aspects of HLA at the time and not just its application to transplantation. After the description of an association between immune response genes and the MHC in mice and guinea pigs by McDevitt and Benacceraf, respectively, I too became interested in the possible association of what we now know as HLA with susceptibility to different diseases. Amiel from Paris had presented some data at the Torino conference suggesting an association between HLA and Hodgkin's disease. As soon as I got established back in Melbourne I commenced a large study of Hodgkins patients from the Cancer Institute and with John Forbes (a young biomedical science student and now Professor of Oncological Surgery at Newcastle University) was able to show a reasonably strong association with HLA (9). Over the next few years I studied quite a number of diseases for possible HLA associations, such as paralytic poliomyelitis where there appeared to be an association with HL-A3 and HL-A7 (old nomenclature) and carcinoma of the lung where there was no association; but the most striking association that I found (with Ian MacKay who was Director of the Clinical Research Unit of the Walter and Eliza Hall Institute) was that between HL-A8 and chronic active hepatitis (10). I also became involved in the anthropological studies of HLA (11). Later, Richard Batchelor (who had come to spend a sabbatical with me) and I went to the highlands of New Guinea as part of the Fifth International Histocompatibility Workshop (12). This was a remarkable time in a remarkable country and our demonstration of the extraordinary limited polymorphism of the HLA system (class I only at that time) made one's mouth water as a transplant surgeon as well as a travelling serologist! During these years I organized anthropological studies of HLA in Southeast Asia, Fiji, and the Australian aborigines, as well as continuing the New Guinea studies (13,14). Alan Ting, my first PhD student, made this the subject of a large part of his thesis. It was a tremendously interesting time in the HLA world.

In Richmond, before I returned to Melbourne, I had also become very interested in the possibility that blood transfusions, which of course in those days were generally given in quite large numbers to patients before transplantation because of anemia, might induce some degree of tolerance. I had looked at this at Richmond but the transfusion data left something to be desired, and so when I came back to Mel-

Richard Batchelor and Peter Morris with Batchelor mascot in 1969 (hence "Bulldog Batchelor").

Jacques Miller and Peter Morris, 1969 in Melbourne, discussing a weighty immunological problem.

NEW GUINEA HIGHLANDS, 1970

Richard Batchelor and Peter Morris with one of the locals.

The Mud Man - HLA?

Peter Morris with enlarged family.

bourne where good transfusion data were available, I was able to look very carefully for an association between prior transfusions and graft outcome. Surprisingly perhaps, bearing in mind that at that time we knew that transfusions could sensitize an individual resulting in the production of leukocyte antibodies, there was no correlation between graft outcome and transfusions, and, in particular, large numbers of transfusions did not lead to a worse graft outcome. In fact there was a suggestion that just the opposite was the case. That led me to write the paper which I still consider one of my better products entitled "The Paradox of Blood Transfusions in Renal Transplantation" (15). Unfortunately, as it was published in the *Medical Journal of Australia*, nobody read it outside Australia!

However, those observations took me to the laboratory to look at the effect of prior blood transfusions on skin allograft survival in the rat. With a young medical student, Hugh Taylor who later became a Professor of Ophthalmology at Johns Hopkins, I carried out large numbers of experiments in which we showed a modest prolongation of survival in rats that had received prior blood transfusions. I remember writing this up and sending it to the *Australian Journal of Experimental Biology and Medical Science*, but they wanted the statistical evaluation changed to a different method. I disagreed with them strongly about this, did not alter it and, indeed, never sent it off anywhere else mainly because the graft prolongation was fairly modest and I did not feel the data were sufficiently different from similar earlier studies by others, including Brent and Medawar.

Then John Fabre joined me, first as a biomedical science student, and after that as a PhD student. We decided to try setting up the vascularized renal transplant model in the rat which had first been described by Sun Lee and then used to demonstrate passive enhancement by Frank Stuart in Boston and Mike French with Richard Batchelor at East Grinstead. The technical aspects of this proved quite difficult to over-

Mammoth Mountain, 1970. Richard Batchelor, Ekkehard Albert, and John McClelland head for the Jacuzzi.

come and transplant after transplant failed. After three or four months without a single success, I remember that I was in bed at home with pneumonia when John Fabre came out to the house to announce triumphantly that a rat had survived the operation with a functioning renal transplant. From there we never looked back and, indeed, I think that the technical success rate in this model in our laboratory was consistently over 90 percent. We also trained technicians to do renal transplants which was considered absolute heresy in the world of surgery! Indeed, the best microsurgical technicians proved to be people who had no experience in medicine or surgery whatsoever and therefore no preconceived ideas about technical expertise. Yoland Lim, a young Chinese, was the first technician, and then Judy McKenzie and Patricia Mottram joined us just out of school and both became superb microsurgeons. Indeed, later on both were to come to Oxford with me in 1974. However, once having established this model we were able to do extensive experiments on blood transfusions as a form of antigen pretreatment and show that one could produce prolonged survival and, indeed, indefinite survival, with different treatment protocols in selected strain combinations (16,17). We were also able to do extensive experiments of passive enhancement in the same model (18-20). However, both from the clinical observations that I had made earlier that prior blood transfusions did not result in poorer graft survival and the experimental data in the rat model, we failed to proceed to the next logical step of deliberately transfusing nontransfused patients before transplantation. This was mainly because of the finding in our rat model that prior transfusions in certain strain combinations sensitized the animal and resulted in accelerated rejection rather than prolonged survival. Then, of course, in 1973, Opelz and Terasaki made the seminal observation that patients who never had any transfusions did badly compared to those who had been transfused. This was, of course, the converse of the observation that I had made in the late 1960s whereby, because virtually no patients had no transfusions at that time, the conclusion was that many transfusions did not lead to poorer graft survival. The transfusion story remains an area of fascination for me as does the whole area of antigen pretreatment and tolerance induction. Today, I still have several groups in the Oxford unit working in this general area of antigen-induced tolerance.

All this time in Melbourne from the end of 1967 to 1974 when I left to go to Oxford, I had been doing clinical surgery as well as running the tissue transplantation laboratories, but it appeared in retrospect that until I went to Oxford, very few of my scientific colleagues outside Australia were aware of the fact that I was a surgeon. It was in 1973 that the next major change in my life was heralded by a phone call from Sir Richard Doll, the Regius Professor at Oxford, asking me whether I would be interested in looking at the Nuffield Chair of Surgery at the University of Oxford. Needless to say, I said I was interested but I must say I did not feel that I would leave Australia for I had only ever been in Oxford for half a day back in 1962, and I had also been offered the Chair of Surgery in Adelaide where there was a thriving transplant unit. On coming to look at Oxford around September time I found there was no transplant unit and also that I really knew none of the surgeons there, my main contacts being Walter and Julia Bodmer, Jim Gowans, and Rod Porter. They were tremendously supportive and encouraged me to come to Oxford where they said the opportunity for good science was second to none and of course they were absolutely right. I had spent two weeks going through the whole set up in Oxford almost brick by brick and meeting every conceivable person that might be involved with the Department of Surgery and the establishment of a clinical and research transplant program. I met the Electoral Board after 10 days or so and was offered the post a few hours after the meeting, which I had decided to say yes to if asked. It was several months before the various conditions that I had requested were satisfied and I was able to finally accept the post just before Christmas in 1973.

Roy Calne had been a member of the Electoral Board and after I arrived at Oxford in August 1974, Roy and Patsy Calne asked Jocelyn, my wife, and me to come over to Cambridge for lunch. I had never been to Cambridge, strange as it might seem, and we drove across country, got hopelessly lost and as a result a two-hour trip took three and a half hours. We arrived at the Calne's home at 2:30 PM, by which time Roy had given up and gone back to work but Patsy, well used to dealing with the unexpected, kept the meal intact and we sat down to lunch close to 3.00 PM. Roy abandoned what he was doing and came home for this rather late lunch before going to play squash to work it off and we wended our way back to Oxford, rather more quickly. That was the first of numerous trips back and forth over the years between Oxford and Cambridge, either Roy coming to Oxford or my going to Cambridge. As we were both tennis players, we established the interdepartmental tennis and squash matches which took place for many years and which were always preceded by a scientific meeting over lunch followed by a match fought to the bitter end. The secret recruiting of the team members by the respective professors generally determined the outcome of the match!

The move to Oxford proved to be a truly unique opportunity for not only was the department (the Nuffield Department of Surgery) rather run down, as my predecessor, Philip Allison, had died just over one year before, but he had left most positions in the department either vacant or due to become vacant and therefore one could only go in one direction, namely upwards. There was also tremendous support on the scientific front especially from Walter Bodmer, Jim Gowans and Rod Porter. I well remember when I was applying for my first program grant from the Medical Research Council, in complete ignorance as to how one went about this in England, being advised quite extensively by Walter Bodmer and David Philips, the Professor of Molecular Biophysics and later to become Chairman of the Associated Board of Research Councils (ABRC), on how to write a Program Grant application. Fortunately, the application was successful and has provided a basic core of support for the whole transplantation biology research program in my department since that date. I had also been fortunate in that several of my technicians from Melbourne agreed to come with me to Oxford and so the laboratories were up and running within weeks of my arriving in Oxford.

However, there was no transplant unit, and so before I came to Oxford I started negotiations with the Department of Health in London (at that time regional centers were funded centrally), but David Owen, who was then Minister of Health in the Labor Government of Harold Wilson, felt that the money he had provided for the establishment of regional transplant centers had been more or less a waste of money, in that the results of transplantation were so bad. The Oxford region was the only region remaining in the country that did not have a transplant center and I gather that he was not at all enthusiastic about providing funding for this last regional unit. However, Walter Bodmer, who knew him quite well, worked on him over luncheon to some good effect for eventually it was agreed that a regional transplant unit would be established at Oxford and in January 1975 the first renal transplant was performed. In 1978 a new transplant unit comprised of six beds in an isolation unit was formally opened by Sir Peter Medawar, by which time the unit was well established and, in-

Cambridge, 1978. Roy Calne and Peter Morris congratulate each other on a fine effort in the Oxford-Cambridge match...who did win?

Roy Calne and Peter Morris, having just completed the dreaded midnight toboggan run together, are glad to be alive.

deed, we had completed two prospective randomized controlled trials; firstly of high-dose steroids in the treatment of rejection and, secondly, of the prophylactic use of high- and low-dose steroids. The introduction of such trials to clinical transplantation was a rare, if not unique, event in those days!

Many exciting developments have occurred in transplantation over these years and I well remember Roy Calne ringing me up sometime in 1977 to tell me about this exciting new drug, cyclosporine. At this stage he had a number of dogs with kidney transplants who had been treated with the drug. When he took me to see the dogs, I must say that they all looked very unwell except for the one dog that kept jumping over the wall and was the one whose slide Roy used to love to show. I wasn't too impressed with cyclosporine, I must say, at least in the dog model where there was obviously a lot of toxicity, but Roy quite rightly picked the one very successful dog as being the true indication of the drug's potential. One must remember that he had been working with renal transplants in dogs using a variety of immunosuppressive agents ever since the early days of his pioneer experiments with 6-mercaptopurine and azathioprine and so was ever alert for the next advance. We started working with cyclosporine in a rodent renal transplant model the following year and performed many experiments studying dosage and timing aspects of cyclosporine together with its mechanism of action in a variety of transplant models (21,22). There was no question that a powerful new immunosuppressive agent was on the horizon and clinically, so it proved to be.

The rat and the mouse microsurgical models of heart, liver, and renal transplantation are still used extensively in our studies of tolerance induction and mechanisms of rejection at the Oxford laboratories. The transfusion story continues to be explored in the experimental model, and not only have we now shown that pretreatment with a single histocompatibility gene product expressed in L cells (transfected with different histocompatibility genes) can induce tolerance to the whole MHC complex of the donor heart (23), but we recently showed that the induction of tolerance by prior transfusion seems to be due to altered regulation of the IL2 pathways (24). Histocompatibility in renal transplantation remains a major interest of my unit. Over the years we have studied the role of sensitization in patients awaiting transplantation extensively and shown that many patients can be transplanted in the presence of positive crossmatches where antibodies are not directed against HLA (25,26). The definition of the different types of antibody in the apparently sensitized patient has allowed us to transplant over 200 sensitized patients with a positive crossmatch at the Oxford unit. In addition, the first demonstration of the striking influence of matching for HLA-DR alone in 1978 proved to be a significant contribution to the matching story in cadaveric renal transplantation (27) and now also in cardiac and pancreatic transplantation.

One of the first new areas of research that I set up on coming to Oxford was that of pancreatic islet transplantation, first in the rodent model then later in large animals with the hope that human islet transplantation would be accomplished in due course (28-30). Of course after the initial description by Lacey and Ballinger of successful islet pancreatic transplantation in the rat it did seem that this might not be too far away, but in fact the preparation of islets from the large mammalian pancreas, including man, proved to be extremely difficult. A significant contribution to this area was made by Derek Gray as a PhD student in the department (now Reader in Transplantation) when he described a successful method of isolating islets from the human pancreas (31). This technique has been adopted by all groups working in this area and now at last some successful islet transplants have been performed in several centers during the last 12 months.

Another major current area of interest has been the role of the dendritic cell in the allo response. Jon Austyn's group has again refined the studies of this fascinating cell and very convincingly shown that the donor dendritic cells from a cardiac allograft migrate to the spleen where they are associated with CD4+ T cells, again suggesting that sensitization to an allograft may take place centrally rather than peripherally (32).

In 1984 I was elected President of The Transplantation Society, succeeding Paul Terasaki, and this undoubtedly was one of the events in my career which gave me the most pleasure. During my presidency several scandals arose concerning the purchase of kidneys from living-unrelated donors, and most of my administrative activities in the Society were concerned with this problem, which was first referred to in my presidential address in Minneapolis on taking up office and then was the sole topic of my second presidential address at Helsinki on leaving office two years later (33,34). I suspect I am and will be the only President of the Society to give two presidential addresses, but my taking office coincided with the change from the new President giving his address at the end of the congress at which he took up office, to giving it in the middle of the Congress for which he was responsible. In any case, the scandals led the Society to tackle these ethical problems posed by living-unrelated transplantation, as outlined in the guidelines issued in 1986, and which continue to be a major area of interest in the Society still today (35).

The past 16 years at Oxford have been a marvelous time in which the Department of Surgery, with the help of many outstanding surgical and scientific colleagues, has developed into a strong and vigorous department. The transplant unit is also firmly established, and, indeed, at this time we are just in the process of moving into our second new building, the Oxford Transplant Center. The transplantation biology research program began modestly with myself and the technicians who came with me from Australia: Wendy Law, Jill Roach, Judy McKenzie, Patricia Mottram, and later Hilary Vaughan. Furthermore, Alan Ting (now Director of Histocompatibility at the Pacific Presbyterian Medical Center in California) who had been my first PhD student in Melbourne before joining Paul Terasaki for five years, came to Oxford to join me in 1977 to take over the tissue typing laboratories. Also John Fabre (now Director of the McIndoe Research Institute), the second PhD student I had in Melbourne, was in England when I came to Oxford on a Royal Society Scholarship during which time he had worked with Richard Batchelor at East Grinstead and then Rodney Porter at the University of Oxford, and he joined my group as a Wellcome Senior Research Fellow, as did Keryn Williams from Melbourne. Andrew McMichael (now MRC Professor of Immunology at the University of Oxford) came back from Stanford to join the department and he was followed later by Ian Hutchinson from Leslie Brent's department (now Professor of Immunology, University of Manchester), Richard Wood (now Professor of Surgery, St. Bartholomew's Hospital, London), and a host of research fellows and graduate students from all over the world, all of whom have made major contributions to the research program. Indeed, the research program in transplantation is comprised of some 70 scientists, graduate students, research fellows, and technicians.

What I have mentioned only reflects a small part of the department's research and clinical activities in transplantation at Oxford over the past 16 years. The present program in transplantation biology is headed by an outstanding team of project leaders; Kathryn Wood, Maggie Dallman, Jon Austyn, Sue Fuggle, and Derek Gray. John Todd heads another group studying the

Minneapolis, 1984. Paul Terasaki has just handed over the Presidency of the Transplantation Society to Peter Morris.

Golf at Pinehurst, 1985, with Randy Bollinger and Fred San Filippo.

molecular genetics of type I diabetes giving me once again an interest, even if rather peripheral, after almost 20 years in HLA and disease. Perhaps what one remembers most are the graduate students, fellows, residents, and visitors who have been through the department during this exciting period when transplantation has been exploding both clinically and in the laboratory, and no doubt this advance will continue at an even faster rate in the coming years. The opportunity to get to know so many in the field of transplantation in every part of the world, including not only those whose reflections are included in this volume, but so many others and especially those in the United Kingdom who have made me so welcome, has given me much pleasure over the past 30 years. As a surgeon and an immunologist I can say that this sometimes schizophrenic existence has allowed me not only to delve into areas that one never would have thought likely in my young surgical training days but, more importantly, has allowed me to mix with clinicians and scientists in all parts of the world, many of whom I count as very good friends, and perhaps that is the best part of it all. Long may it continue.

REFERENCES

1. Morris PJ, Burke JF. Antilymphocyte serum and staphylococcal infection. Nature 1967; 214:1138.
2. Morris PJ, Bondoc C, Burke JF. The use of frequently changed skin allografts to promote healing in the non-healing infected ulcer. Surgery 1966; 60:13.
3. Morris PJ, Hume DM, Terasaki PI. The development of cytotoxic antibodies in renal transplantation. In: Curtoni ES, Mattiuz PL, Tosi RM, Eds. Histocompatibility Testing 1967. Munksgaard, Copenhagen, 1967; 339.
4. Morris PJ, Williams GM, Hume DM, et al. Serotyping for homotransplantation. XII. Occurrence of cytotoxic antibodies following kidney transplantation in man. Transplantation 1968; 6:392.
5. Williams GM, Hume DM, Hudson RP Jr., et al. "Hyperacute" renal-homograft rejection in man. N Engl J Med 1968; 279:611.
6. Williams GM, Morris PJ, Harlan WR, Hume DM. Serological studies in transplant recipients with the nephrotic syndrome. In: Dausset J, Hamburger J, Mathe G, Eds. Advance in Transplantation. Munksgaard, Copenhagen, 1967; 373.
7. Morris PJ, Kincaid-Smith P, Ting A, et al. Prospective leucocyte typing in cadaver renal transplantation. Lancet 1968; 2:803.
8. Loewenthal J, Kincaid-Smith P, Lawrence JR, et al. Australian national dialysis and renal transplantation survey. First report of a sub-committee. Lancet 1970; 1:744.
9. Forbes JF, Morris PJ. Leucocyte antigens in Hodgkin's disease. Lancet 1970; 2:849.
10. Mackay IR, Morris PJ. Association of autoimmune active chronic hepatitis with HL-A1,8 Lancet 1972; 2:793.
11. Morris PJ, Ting A, Alpers MP, Simons M. Leukocyte antigens in a New Guinea population. Tissue Antigens 1971; 1:49.
12. Morris PJ, Bashir H, McGregor SA, et al. Genetic studies of HL-A in New Guinea. In: Dausset J, Colombani J, Eds. Histocompatibility Testing. Munksgaard, Copenhagen, 1972; 267.
13. Ting A, Wee GB, Simons MJ, Morris PJ. The distribution of HLA leucocyte antigens in Singapore Chinese, Malays and Indians. Tissue Antigens 1971; 1:258.
14. Ting A, Morris PJ. Relationship of six ethnic groups based on the HL-A system. In: Dausset J, Colombani J, Eds. Histocom-

patibility Testing. Munksgaard, Copenhagen, 1972; 275.

15. Morris PJ, Ting A, Stocker J. Leucocyte antigens in renal transplantation. I. The paradox of blood transfusions in renal transplantation. Med J Aust 1968; 2:1088.

16. Fabre JW, Morris PJ. The effect of donor-strain blood pretreatment on renal allograft rejection in rats. Transplantation 1972; 14:608.

17. Fabre JW, Morris PJ. The mechanisms of specific immunosuppression of renal allograft rejection by donor strain blood. Transplantation 1972; 14:634.

18. Fabre JW, Morris PJ. Experience with passive enhancement of renal allografts in a (DA X LEWIS)F1 to LEWIS strain combination. Transplantation 1972; 13:604.

19. Batchelor JR, Fabre JW, Morris PJ. Passive enhancement of rat kidney allografts: potentiation with antithymocyte serum. Transplantation 1972; 13:610.

20. Fabre JW, Morris PJ. Dose response studies in passive enhancement of rat renal allografts transplantation. Transplantation 1973; 15:397.

21. Homan WP, Fabre JW, Morris PJ. Nature of the unresponsiveness induced by cyclosporin A in rats bearing renal allografts. Transplantation 1979; 28:439.

22. Homan WP, Fabre JW, Williams KW, et al. Studies of the immunosuppressive properties of cyclosporin A in rats receiving renal allografts. Transplantation 1980; 29:361.

23. Madsen JC, Superina RA, Wood KJ, Morris PJ. Immunological unresponsiveness induced by recipient cells transfected with donor MHC genes. Nature 1988; 332:161.

24. Dallman MJ, Shiho O, Page TH, et al. Peripheral tolerance to alloantigen results from altered regulation of the Interleukin-2 pathway. J. Exp Med 1991; 173:79.

25. Morris PJ, Ting A, Daar AS, Oliver D. B-cell alloantibodies and renal allografts. Lancet 1976; 2:312.

26. Ting A, Morris PJ. Renal transplantation and a B-cell cross-match with autoantibodies and alloantibodies. Lancet 1977; 2:1095.

27. Ting A, Morris PJ. Matching for B-cell antigens of the HLA-DR (D-related series) in cadaver renal transplantation. Lancet 1978; 1:575.

28. Finch DRA, Morris PJ. Passive enhancement of isolated pancreatic islet allografts. Transplantation 1976; 22:508.

29. Finch DRA, Wise PH, Morris PJ. Successful intra-splenic transplantation of syngeneic and allogeneic isolated pancreatic islets. Diabetologia 1976; 13:195.

30. Du-Toit DF, Reece-Smith H, McShane P, et al. Effect of Cyclosporin A on allotransplanted pancreatic fragments to the spleen of totally pancreatectomized dogs. Transplantation 1982; 33:302.

31. Gray DWR, McShane P, Grant P, Morris PJ. A method for isolation of islets of Langerhans from the human pancreas. Diabetes 1984; 33:1055.

32. Larsen CP, Morris PJ, Austyn JM. Migration of dendritic leukocytes from cardiac allografts into host spleens. A novel pathway for initiation of rejection. J Exp Med 1990; 171:307.

33. Morris PJ. Presidential Address: Transplantation Society, 1984. Transplant Proc 1985; 17:1615.

34. Morris PJ. Problems facing The Society today: Presidential Address, Transplantation Society 1986. Transplant Proc 1987; 29:16.

35. The Council of the Transplantation Society. Commercialisation in transplantation: The problems and some guidelines for practice. Lancet 1985; 2:715.

CURRICULUM VITAE

Peter J. Morris

PERSONAL

Born:	April 17, 1934; Horsham, Victoria, Australia
Marital Status:	Married (Jocelyn); 5 children (Peter, Sarah, James, Elizabeth, Michael)
Office Address:	Nuffield Department of Surgery John Radcliffe Hospital Oxford, OX3 9DU

EDUCATION

1957	Melbourne, B.S., M.B.
1972	Melbourne, Ph. D.
1974	Oxon, M.A.
1962	Fellow of the Royal College of Surgeons of England
1968	Fellow of the Royal Australasian College of Surgeons
1969	Fellow of the American College of Surgeons

POSITIONS

1958-61	Resident Medical Officer, Senior House Officer and Surgical Registrar, St. Vincent's Hospital, Melbourne, Australia
1961	Dominion Postgraduate Fellowship, Guy's Hospital, London
1962	Surgical Officer, Royal Postgraduate Medical School, London
1963	Surgical Registrar, Southampton General Hospital, Southampton
1964	Senior Assistant Surgical Resident, Massachusetts General Hospital, Boston, Massachusetts
1965-66	Clinical and Research Fellow in Surgery, Harvard Medical School and Massachusetts General Hospital, Boston, Massachusetts
1967	Assistant Professor of Surgery, Medical College of Virginia, Richmond
1968-74	Director of the Tissue Transplantation Laboratories, Department of Surgery, University of Melbourne, The Royal Melbourne Hospital, Melbourne, Australia
1968-74	Honorary Consultant to the Experimental Pathology Unit, Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia
1971-74	Reader in Surgery and First Assistant, Department of Surgery, University of Melbourne Royal Hospital, Melbourne, Australia
1974-	Nuffield Professor of Surgery and Chairman,Department of Surgery, University of Oxford, John Radcliffe and Churchill Hospitals, Oxford
1974-	Director of Oxford Transplant Centre, Churchill Hospital
1974-	Honorary Consultant Surgeon, Oxford Health Authority
1974-	Fellow of Balliol College, Oxford University

AWARDS

1971	The Selwyn Smith Prize of the University of Melbourne, awarded for the most significant contribution to Medical Research during the three years preceding the award (shared with Dr. M. Denborough)
1972	Hunterian Professorship of the Royal College of Surgeons of England
1976	Honorary Life Membership of the Australian Society of Nephrology
1982	Honorary Life Membership of the Transplantation Society of Australia and New Zealand
1982	Honorary Fellowship of the American Surgical Association
1986	Honorary Fellowship of the American College of Surgeons
1987	Honorary Fellowship of the Society of Clinical Surgery
1988	Cecil Joll Prize of the Royal College of Surgeons of England for outstanding contributions to transplantation and vascular surgery
1989	Honorary Fellowship of the Asian Surgical Society

EDITORIAL BOARDS AND EDITORSHIPS

Transplantation
Transplantation Reviews
Tissue Antigens
Australian and New Zealand Journal of Surgery
World Journal of Surgery
Surgery, Gynecology and Obstetrics
Asian Surgical Association

COUNCIL AND ADVISORY COMMITTEE MEMBERSHIPS

1970-	Councillor, International Histocompatibility Society
1973-74	Director, Australian Kidney Foundation
1974-85	Member, World Health Organization Expert Advisory Panel on Immunology
1976-79	Chairman, British Transplantation Society
1980-82	Vice-President, Transplantation Society
1982-84	President Elect, Transplantation Society
1984-86	President, The Transplantation Society
1983-87	Member of Council, Medical Research Council
1986-90	Chairman, National Kidney Research Fund
1989-	University Funding Council, Medical Committee

PUBLICATIONS

Kidney Transplantation: Principles and Practice 1st edit. 1979, 2nd edit. 1984, 3rd edit. 1988 (W.B. Saunders, Philadelphia) and 12 other books.

550 scientific articles, chapters, and reviews

HISTORY OF TRANSPLANTATION

Rudolf Pichlmayr

Address: Klinik für Abdominal- und
Transplantationschirurgie
Medizinischen Hochschule Hannover
Konstanty-Gutschow Str. 8
3000 Hannover 6
Germany

Rudolf Pichlmayr

1965

1990

HISTORY OF TRANSPLANTATION

Rudolf Pichlmayr

Introduction

It was Dr. Willem Kolff's visit to Munich in the early 1960s that fascinated me. I was in training as a resident under Professor Dr. Rudolf Zenker in the Department of Surgery at the University when Dr. Kolff lectured about the potential of artificial organs and organ transplantation. Nearly 30 years later, I am still aware of the decisive influence that a guest lecturer may have on some individuals in the auditorium, particularly the younger ones. Rarely will the lecturer become aware of this influence and its consequences. Therefore, at the beginning of this chapter I would like to gratefully mention the many excellent and impressive lectures and presentations by pioneers in organ transplantation which I had the privilege to hear over the years. I think the first decades of organ transplantation were characterized not only by an enormous scientific work in medicine and biology, but also by a profound and exhaustive consideration of the ethical implications of this new field. It is remarkable that this has been done mainly by the clinicians themselves in cooperation with other scientists, a point to which I will return later.

Dr. Kolff reported on progress in artificial renal replacement and on the early results of clinical kidney grafting in the United States. By today's standards, the outcome of those patients appears unsatisfying, but the results clearly proved that a cadaver organ could save the life of another human being. I remember very well my somewhat ambiguous feelings: on the one hand, I was fascinated by the possibility for success, but on the other, I had the impression that the principal problems of this new therapy had already been solved and that it would be difficult, if not impossible, to contribute to this field as a young surgical resident in Germany. Prerequisites and resources for both basic and clinical research were extremely restricted in those days. Thus, some disappointment was mixed with my admiration of the epochal events. Frankly, this feeling arose frequently in later days, but I think it is justified: we have to accept, and we acknowledge, that the major steps in research and its clinical application during and after World War II were accomplished in the Anglo-American world. Thus, after first mentioning the important influences of great speakers, I will emphasize the outstanding and continuous contribution of the Anglo-American scientists and clinicians, frequently unified in one person. With this in mind, I thought, not only retrospectively but also, in part, prospectively, that my main goals would be:

-to deepen some scientific fundamentals;

-to try to combine in clinical practice quality with quantity in order to help more people;

-to promote organ transplantation, particularly in my own country;

-to find facilities to enable young coworkers to perform high-quality research.

Some steps on this certainly always difficult but inspired way are mentioned briefly in the following account.

Early Experimental Work - Antilymphocyte Serum

As mentioned above, the possibilities for research were limited and difficult; well-planned programs did not exist. Identifying scientific problems which could be approached successfully, establishing appropriate methods, and looking for grants were the responsibility of the individual who wanted to do research. The autodidactic

The Munich ALG-Group in 1966: Rudolf Pichlmayr, Christa Schülgen, Walter Brendel, Walter Land.

Gerd Tidow with the first successfully ALG-treated dog, Gunther.

approach and lack of continuity certainly were and are one reason for lower research productivity in our country. I have been lucky in that my Surgical Chief, Rudolf Zenker, tried intensely to advance surgical research. He initiated the foundation of a Chair for Experimental Surgery in Munich and recruited Walter Brendel for this task. I was one of the first surgical residents with the opportunity to work with Walter Brendel in his first institute, the hospital's bomb-shelter. I could be relieved of clinical duties for exactly one year, which was the maximum time for research. It was a highly active period. My assignment was to do research "in organ transplantation." But which field and which question could be worked out satisfactorily within one year? I studied the literature on transplantation intensively and together with Gerd Tidow and Kurt Wonigeit, two young students who later became coworkers for many years, began to work on a goal that is still our dream today: to induce tolerance.

Aware that antigen-induced neonatal tolerance could eventually be achieved in adults with overwhelming doses of antigen (1), we injected mice intravenously (!) with large amounts of allogeneic (in those days called homologous) liver and spleen homogenates produced by sonification and lyophilization. Of course, the animals were very sensitive to these massive injections, which had to be performed extremely slowly - by hand and over hours into the tail vein. During this procedure, the animals were kept in specially constructed cages for at least eight days. Thus, an aliquot from an entire liver or spleen could be injected into a single animal. Indeed, skin grafts performed some days later (done accurately according to the method of Billingham and Medawar) (2) showed a specifically prolonged survival from two to seven days in several animals. Interestingly, there was no hyperacute rejection.

But what should we do with those results? As a surgeon, I had to find something "worthwhile." Those experiments could hardly be transferred into humans. Our immunological armatory and knowledge at that time was insufficient to work out mechanisms for the prolonged graft survival. The amount of foreign antigen administered was so high that a further increase seemed impossible; tolerance could hardly be expected by this method.

About this time, I read a paper by Michael Woodruff about the production and the effect of an antilymphocyte serum in rats (3). Could this be a method applicable to humans? I left mice and rats and turned to dog experiments, classified - perhaps correctly - as "preclinical" models, but actually more appropriate for a surgeon.

To make a long story short: we worked with intensity to produce a specifically "pure" antilymphocyte serum, the first of which was horse-antidog. After experimental success it was followed immediately by a horse-antihuman serum. These sera were unique in that they were obtained by immunization with lymphocytes derived only from thoracic duct drainage and anti-erythrocyte antibodies had been intensively absorbed (4,5). Even today I would not rule out the possibility that this particular type of immunization with freshly prepared viable recirculating lymphocytes may have contributed to the high potency of these early antisera: several kidney transplanted dogs treated solely with daily intravenous injections of antilymphocyte sera lived significantly longer than untreated controls. One of the first transplanted dogs, Gunther (all animals were individually named), lived many years with the family of Gerd Tidow and was free of immunosuppression after having been treated for one year with daily intravenous injections of 10 ml horse-anti-dog-antilymphocyte serum. Was this tolerance?

Rudolf Pichlmayr trying to explain immune processes in his thesis, 1967.

ALG-discussion in Capetown following the first human heart transplantation: Hans-Georg Borst, Walter Brendel, Christiaan Barnard.

Ten-year Anniversary of Eurotransplant Foundation in 1978: Jon van Rood, Rudolf Pichlmayr, Bernhard Cohen, Guido Persijn.

Everyone, including my wife, friends of the coworkers, technicians, etc, worked extremely hard. The admirable unselfishness of all is not forgotten but cannot be acknowledged in detail here. All our experiments had to be done initially without grant support because the application was considered unpromising by the committee. Fortunately, I obtained horses for immunization from Drs. G. Beck and E. Schmittdiel, the Directors of the Bayerische Landesanstalt für Tierseuchenbekämpfung München-Schleißheim, without any payment. This was a truly invaluable help. I think that in today's more organized and regulated circumstances, all of these experiments would require a much longer period.

Through all of these difficulties and many setbacks, two famous scientists helped me tremendously: Sir Michael Woodruff and Sir Peter Medawar. Although I was an unknown surgical resident, both received me personally and spoke with me in an unforgettable way. I learned that it may be an attribute of really great men to offer time to those who need their help, regardless of their own workload.

But even at this stage of experimental success in dogs with kidney transplants and soon after with liver transplants, experts completely ignored the fact that injection of heterologous sera into humans could be successfully performed, particularly over prolonged periods. It was argued that this had never been done previously and that anaphylaxis would certainly occur. However, the urgency of the clinical situation was stronger than the well-founded theoretical objections: kidney graft loss due to rejection at this time exceeded 30 percent; furthermore, immunosuppression itself was highly dangerous. In addition, our experiments demonstrated a reduction of hypersensitive reactions and suppression of humoral antibodies following long-term continuation of antiserum administration, justifying application of this therapy to humans. Thus, with full agreement by the patients, we repeatedly injected horse-antihuman thoracic duct lymphocyte sera intravenously into kidney patients. Soon, trials were performed in patients with severe cases of myasthenia gravis with some interesting and promising effects. But in the absence of other immunosuppressive treatment increasing hyperergic reactions occurred. It was at this time that Thomas Starzl in Denver independently began intramuscular injections of antispleen lymphocyte antisera (6).

In 1968, Christiaan Barnard performed the first heart transplantation on the patient Blaiberg, who subsequently developed a rejection crisis. Walter Brendel and Hans-Georg Borst hurried to Capetown with our antilymphocyte serum, which was then used for Blaiberg and the following patients; I stayed in Munich, immunizing and bleeding more horses for further supply!

Thus, the highly stimulating period of immunosuppression by antibodies was opened. Interestingly enough, many of the old questions regarding the true effect of the antibodies - lymphocyte destruction, opsonization, coating, "sterile activation," selective effects on recirculating cells - and the details of an optimum type of immunizing cells and of immunizing and purification protocols have never been answered completely. Despite the availability of monoclonals, polyclonal antilymphocyte antibodies are still in use; however, there is no uniform polyclonal antilymphocyte preparation: "The" antilymphocyte serum does not exist.

Those early days in experimental and clinical organ transplantation were not only demanding, requiring great effort and frequently improvised and primitive methods, but were extremely stimulating as well. So many fields had to be covered by thoughts, discussions, and experiments simultaneously. Most things were new, but solutions seemed to be available; for example, even Sir Peter Medawar thought that the problem of severe rejection would be solved within a few years by the rapidly developing knowledge about histocompatibility. For a young surgeon it was a highly exciting phase. Walter Brendel stands out as a personification of the intensity and productivity of this time, and the transplant community, particularly in my own country, owes him much.

Establishment of Clinical Transplantation in Hannover

When I received the opportunity to move to the new medical school in Hannover with Hans-Georg Borst in 1968, we tried to establish clinical kidney transplantation immediately. However, the first renal transplantation, performed with the techniques used at that time, failed due to hyperacute rejection in spite of a negative crossmatch. The relatively small number of transplants carried out during the first few years (about 10-15 each year) reflects the many difficulties and problems which had to be solved before organ transplantation could be established: the public had to be informed continuously about this new method and its various implications. All who went through this stage remember how critical many physicians and nephrologists had been, how difficult it was to win the support and cooperation of colleagues, and to convince ethical experts and lawyers of the merit of organ transplantation. A visit from Charly Gelin provided psychological support during a critical period. His already advanced experience and his well-known optimism and sparkling wit stimulated many colleagues.

Since then, over the next two decades, the standing of organ transplantation has changed completely: initially thought to be a somewhat exotic idea with limited clinical relevance, propagated by a few medical visionaries, today a complete transplant program is considered mandatory for every medical school and even for some large city hospitals. Our initial thinking was wrong, but the latter development seems problematic. Overestimating the importance of organ transplantation risks neglecting other important medical fields; furthermore, an excessively widespread transplant practice may not always be linked with adequate experience and continuous adaptation of knowledge in this still rapidly developing field. The concentration within transplant centers seems to be more promising when surgeons and internists, along with experts in a wide range of other important disciplines, are clinically and scientifically oriented toward this field. One prerequisite for such a structure is general acceptance of intensive cooperation in the organ donation program from all physicians, whether or not they are members of institutions with transplant centers. Furthermore, organ transplantation must be regarded as a specialty like other medical fields, best performed by experts.

To date, more than 2,000 kidneys, over 600 livers, 372 hearts, 25 lungs, and several pancreatic organs have been transplanted in Hannover, and organ transplantation is indeed a major interest of the medical school. I am extremely thankful to many colleagues and institutions in Hannover for their cooperation and help. As capacity limits were reached some time ago, we wait for a new building, a "Transplant Center" for all kinds of transplantations including specialized research units. This would also provide the opportunity to develop new organizational structures for transplant medicine. Hereby, the important question arises: whether a surgeon working there will be "only" a transplant surgeon with specialization for particular organs or whether he will also work as a general or cardiac surgeon. For the present generation of transplant surgeons - and I think for the development of the field of transplantation in general - the wider experience is necessary. Will this also hold true for the next generation, or will further developments mainly depend on a high degree of specialization combined with profound knowledge in advanced fundamental research, such as molecular biology?

Perhaps both ways will have their justification and their importance. For example, the wide spectrum of abdominal surgery was - and probably will continue to be - essential to our liver transplant program. Thus, resection therapy for liver tumors or central bile duct tumors could be extended and compared with the chances of liver transplantation (7,8). Experience in hepatic transplantation allowed the introduction of ex-situ liver surgery (8,9). Training in liver resection facilitated the application and further development of segmental liver grafts (10) and the first "splitting procedure" - the use of one donor liver for two recipients (11). This splitting technique was developed independently shortly thereafter by Henri Bismuth (12), who is also a well known expert in liver surgery and liver transplantation; this technique has since been used frequently by Christoph Broelsch, my former coworker, in Chicago (13). Similarly, the technique and strategy of total hepatectomy for acute liver failure with toxic effects (14), severe trauma with subsequent hepatic transplantation after an anhepatic phase (15), different types of portal reperfusion (16), or auxiliary liver transplantation (17), required experience in hepatic as well as abdominal surgery. The same is true for the various forms of combined transplantations (18) or the cluster technique (19).

These potentials are certainly not limited to the present, and wide surgical experience including continuous training will also be mandatory for future transplant surgeons. On the other hand, relevant clinical research increasingly demands the use of basic research technology - certainly more than I had when experimenting with antilymphocyte sera or antigen overloading! Thus, I am specifically grateful to Kurt Wonigeit, who has been working with me both clinically and experimentally for such a long time. Our goal has been to create a clinically-oriented transplant research unit to improve the conditions for training young surgeons in applied immunology based on appropriate and advanced techniques. Major topics of the group in the past have been the analysis of donor-specific T-cell responses after liver and kidney transplantation (20,21), the effect of major and minor histocompatibility barriers on pancreas and heart transplants in the rat (22), and changes in the expression of MHC and adhesion molecules in human and rat allografts under various conditions (23,24). Other areas of interest have been the immunosuppressive effect and the clinical relevance of cyclosporine metabolites (25), the in vivo and in vitro effects of a monoclonal antibody to the T-cell receptor (26,27), and the cytological monitoring of liver allograft rejection by flow cytometry and fine needle biopsy (28,29). To a large extent, this scientific work could be skillfully done by young surgical fellows during research periods and continued during their subsequent clinical training. Such structures will facilitate research for clinicians. I predict that some of these surgeons, trained in basic research and scientifically active as well, will finally confine themselves to some clinical transplant specialty to deepen their scientific work. Thus, they will follow the second way mentioned above. Universities, therefore, will have to establish appropriate organizational facilities to allow for the possibility of either way.

Ethical Implications

The introduction and establishment of clinical organ transplantation had to be accompanied by ethical considerations. I would like to express my appreciation to the many philosophers, jurists, theologists, practicing priests, and other experts dealing with ethical questions with whom we surgeons could discuss in depth all the implications. A deeper understanding was the principal result. Furthermore, brain death - a medical and not an ethical or philosophical phenomenon, but one of immense psychological implication - is now widely accepted because of the circumspect explanation and argumentation of neurologists and many others. In Germany, a recent joint declaration of the Protestant Church and the Roman Catholic bishops supporting the idea of organ donation and acknowledging the justification and value of organ transplantation was agreed upon and published (30). Similar declarations have been made in many countries by public institutions. Thus, organ transplantation has become highly accepted throughout the world within the last two to three decades. This would not have been possible without public confidence in the strict ethical correctness in all aspects and steps of organ transplantation, particularly in the responsibility of the surgeons. The essential ethical concerns in organ donation include: optimal treatment for a potential donor aimed at saving his life; certain diagnosis of brain death before organ explantation; consent from the donor or his family to use the necessary organs; and avoidance of harming the feelings of relatives and other persons concerned with either words or circumstances. In living organ transplantation, volunteerism of the organ donation after thorough information of the potential donor is the most important prerequisite.

Undoubtedly, the behavior of all persons involved in organ explanation and transplantation procedures must meet high ethical standards (31). Thus far, I think a high ethical standard has been kept. There may have been exceptions, but they have been limited and uniformly condemned by the international transplant community.

There are, however, some dangers of which we should be aware. While clear commercialization has been rejected by the vast majority of the transplant community, some intermediate stages between pure altruism and selling organs have appeared. The term "financial incentive" is discussed frequently. I think we have to be extremely cautious. In this context, I would like to mention that those dangerous discussions are generally not brought up by physicians, particularly not transplant surgeons, but instead by ethicists. This is perhaps promoted and facilitated by the many meetings on the ethical aspects of organ transplantation in recent times. I don't want to be misunderstood; organ transplantation, with all of its steps and developments, has to be accompanied by careful discussions about ethical implications. As mentioned above, we are fortunate that this was done by highly qualified experts. A solid foundation has been laid. Let us watch carefully for solid arguments regarding change. Now that organ donation has been realized, we who mediate this humane help - the donated organ - from donor to recipient have the final responsibility for correctness.

REFERENCES

1. Mitchison NA. Induction of immunological paralysis in two zones of dosages. Proc R Soc (Biol) 1964; 161:275.
2. Billingham RE, Medawar PB. The technique of free skin grafting in mammals. J Exp Biol 1951; 28:385.
3. Woodruff MFA, Anderson NF. The effect of lymphocyte depletion by thoracic duct fistula and administration of antilymphocytic serum on the survival of skin homografts in rats. Ann NY Acad Sci 1964; 120:119.
4. Pichlmayr R. Herstellung und Wirkung heterologer Antihundelymphozytenseren. Z Gesamte Exp Med 1967; 143:161.
5. Pichlmayr R, Brendel LJ, Zenker R. Production and effect of heterologous anti-canine lymphocyte serum. Surgery 1967; 61:774.
6. Starzl TE, Marchioro TL, Porter KA, et al. The use of heterologous antilymphoid agents in canine renal and liver homotransplantation and in human renal homotransplantation. Surg Gynecol Obstet 1967; 124:301.
7. Pichlmayr R, Ringe B, Lauchart W, et al. Radical resection and liver grafting as the two main components of surgical strategy in the treatment of proximal bile duct cancer. World J Surg 1988; 12:67.
8. Ringe B, Wittekind C, Bechstein WO, et al. The role of liver transplantation in hepatobiliary malignancy: a retrospective analysis of 95 patients with particular regard to tumor stage and recurrence. Ann Surgery 1989; 209:88.
9. Pichlmayr R, Bretschneider HJ, Kirchner E, et al. Ex situ Operation an der Leber. Eine neue Möglichkeit in der Leberchirurgie. Langenbecks Arch Chir 1988; 373:122.
10. Ringe B, Pichlmayr R, Burdelski M. A new technique of hepatic vein reconstruction in partial liver transplantation. Transplant Int 1988; 1:30.
11. Pichlmayr R, Ringe B, Gubernatis G, et al. Transplantation einer Spenderleber auf zwei Empfänger (Splitting-Transplantation) - Eine neue Methode in der Weiterentwicklung der Lebersegmenttransplantation. Langenbecks Arch Chir 1988; 373:127.
12. Bismuth H, Morino M, Castaing D, et al. Emergency orthotopic liver transplantation in two patients using one donor liver. Br J Surg 1989; 76:722.
13. Emund JC, Whitingon PF, Thistlethwaite JR, et al. Transplantation of two patients with one liver. Ann Surg 1990; 212:14.
14. Ringe B, Pichlmayr R, Lübbe H, et al. Total hepatectomy as temporary approach to acute hepatic or primary graft failure. Transplant Proc 1988; 20(1):552.
15. Ringe B, Pichlmayr R, Ziegler H, et al. Management of severe hepatic trauma by two-stage total hepatectomy, and subsequent liver transplantation. Surgery (in press).
16. Pichlmayr R, Gubernatis G, Grosse H, et al. Lebertransplantation bei niedrigem Pfortaderfluß: Separation beider Pfortaderbereiche mit getrennter portal-venöser und arterialisiert-caval-venöser Leberperfusion. 1. Klinischer Bericht. Langenbecks Arch Chir 1989; 374:232.
17. Gubernatis G, Pichlmayr R, Kemnitz J, et al. Auxiliary partial orthotopic liver transplantation (APOLT) for fulminant hepatic failure - first and successful case report. (submitted).
18. Wallwork J, Williams R, Calne RY. Transplantation of liver, heart and lungs for primary biliary cirrhosis and primary pulmonary hypertension. Lancet 1987; 1:182.
19. Starzl TE, Todo S, Tzakis A, et al. Abdominal organ cluster transplantation for the treatment of upper abdominal malignancies. Ann Surgery 1989; 210:374.

20. Wonigeit K, Pichlmayr R. Specific defect in the capability to generate cytotoxic effector cells in vitro after organ transplantation in man. Dialysis Transplant 1977; 6:58.

21. Schwinzer R, Wonigeit K, Nashan B, et al. Selective increase of CD8+CD11+Cells in long-term liver allograft recipients. Transplant Proc 1987; 19:3812.

22. Klempnauer J, Wonigeit K, Steiniger B, et al. Pancreas whole organ transplantation in the rat: Differential effect of individual MHC regions. Transplant Proc 1983; 15:1308.

23. Steiniger B, Klempnauer J, Wonigeit K. Altered distribution of class I and class II MHC antigens during acute pancreas allograft rejection in the rat. Transplantation 1985; 40:234.

24. Steinhoff G, Wonigeit K, Pichlmayr R. Analysis of sequential changes in MHC expression in human liver grafts after transplantation. Transplantation 1988; 45:394.

25. Schlitt HJ, Chrishans U, Bleck J, et al. Contribution of cyclosporin metabolites to immunosuppression in liver-transplanted patients with severe graft dysfunction. Transplant Int 1991; 4:38.

26. Wonigeit K, Nashan B, Schwinzer R, et al. Use of a monoclonal antibody against the T cell receptor for prophylactic immunosuppressive treatment after liver transplantation. Transplant Proc 1989; 21:2258.

27. Nashan B, Wonigeit K, Schwinzer R, et al. Fine specificity of a panel of antibodies against the TCR/CD3 complex. Transplant Proc 1987; 19:4270.

28. Winkler M, Schwinzer R, Wonigeit K. Patterns of MHC class II antigens expression (HLA-DR, DP, and DQ) on peripheral blood T lymphocytes in patients after liver transplantation. Transplant Proc 1989; 21:3627.

29. Schlitt HJ, Nashan B, Wittekind C, et al. Differentiation of liver graft dysfunction by transplant aspiration cytology. Transplantation 1991; 51:786.

30. Erklärung der Deutschen Bischofskonferenz und des Rates der Evangelischen Kirche in Deutschland. Organtransplantation 2nd July, 1990.

31. Arbeitsgemeinschaft der Transplantationszentren in der Bundesrepublik Deutschland einschl. Berlin-West e. V. Transplantationskodex 13th Nov, 1987.

CURRICULUM VITAE

Rudolf Pichlmayr

PERSONAL

Born: May 16, 1932; Munich, Germany

Marital Status: Married since October 10, 1955 to Professor Dr. Ina Pichlmayr, geb. Rohrmann, Director of Section for Anesthesiology, Städtisches Krankenhaus Oststadt, Medizinische Hochschule Hannover; 5 children

Home Address: Blumenweg 3, 3002 Bissendorf-Wietze

Office Address: Klinik für Abdominal- und Transplantationschirurgie der Medizinischen Hochschule Hannover Konstanty-Gutschow-Str. 8 3000 Hannover 61

EDUCATION

1951-56	Medical School, University of Munich
1956	Doctor's thesis
1958-59	Department of Pathology, Krankenhaus rechts der Isar in Munich, Prof. Dr. L. Burkhardt
1959	License to practice medicine
1959-60	Department of Surgery, Krankenhaus rechts der Isar in Munich, Prof. Dr. G. Maurer
1960-68	Department of Surgery, University of Munich, Prof. Dr. h.c. R. Zenker
1964	Surgical board license
1967	Ph.D. in Surgery Dissertation on "Production and Effects of Heterologous Antidog-Antilymphocyte Sera" Z. ges. exp. Med. 143, 161-226, 1967
1968	Transferal of academic grades from Munich to Hannover
1969	Appointment as Associate Professor and Director of Abdominal Surgery at the Medizinische Hochschule Hannover
1973	Appointment as Full Professor: Chair for Abdominal and Transplantation Surgery at the Medizinische Hochschule Hannover

POSITIONS

1974-78	Dean of Continuing Education
1984-	Chairman of Ethics Committee
1986-	Speaker of the Conjoint Grant Proposals for the Deutsche Forschungsgemeinschaft in Hannover for "Development of Clinical Transplantation of Liver, Heart and Lung"
1989-	Dean for Research, Scientific Affairs and Promotions

PROFESSIONAL SOCIETIES

Deutsche Gesellschaft für Chirurgie
Sektion Experimentelle Chirurgie der Deutschen Gesellschaft für Chirurgie
Vereinigung Bayerischer Chirurgen
European Society for Surgical Research
Transplantation Society
Gesellschaft Deutscher Naturforscher und Ärzte
Collegium Internationale Chirurgie Digestivae
Société Internationale de Chirurgie
Gesellschaft für Immunologie
European Dialysis and Transplant Association
Kuratorium für Dialyse und Nierentransplantation
Deutsche Krebshilfe
Gesellschaft für Gastroenterologie in Bayern
European Society for Organ Transplantation
Gesellschaft zur Förderung Biomedizinischer Forschung
Akademie für Ethik in der Medizin
Berliner Chirurgische Gesellschaft
Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten

HONORARY MEMBERSHIPS

1986	Deutsche Akademie der Naturforscher LEOPOLDINA
1987	Korrespondierendes Mitglied der Österreichischen Gesellschaft für Chirurgie
1988	Honorary Fellowship of Royal College of Surgeons of England
1990	Honorary Fellowship of American College of Surgeons

AWARDS

1968	VON LANGENBECKS-Preis der Deutschen Gesellschaft für Chirurgie
1983	ERICH LEXER-Preis der Deutschen Gesellschaft für Chirurgie
1985	ERNST JUNG-Preis für Medizin der Ernst Jung-Stiftung für Wissenschaft und Forschung
1985	Verleihung der NIEDERSÄCHSICHEN LANDES MEDAILLE
1987	Preis der LUCIE BOLTE-Stiftung
1987	NIEDERSACHSENPREIS für Wissenschaft der Niedersächsischen Landesregierung
1990	JATROS-Preis für den Mediziner des Jahres

EDITORIAL BOARDS AND EDITORSHIPS

- Der Chirurg
- World Journal of Surgery
- Transplantation Proceedings
- Clinical Transplantation
- Zeitschrift für Transplantationsmedizin
- Transplante of Organs and Tissues

COUNCIL AND ADVISORY COMMITTEE MEMBERSHIPS

1975-	Wissenschaftlicher Beirates des Kuratorium für Dialyse und Nierentransplantation, member
1975-79	Arbeitskreis "Organtransplantation" des Wissenschaftlichen Beirates der Bundesärztekammer, chairman
1975-85	Wissenschaftlicher Beirat der Bundesärztekammer, member
1977-	Executive Board Committee of Eurotransplant Foundation, Leiden, member
1978-80	Sektion Experimentelle Chirurgie der Deutschen Gesellschaft für Chirurgie, chairman
1980-85	Vorstand des Wissenschaftlichen Beirates der Bundesärztekammer, member
1984-	Vorstand des Stiftungsrates der Deutschen Stiftung Organtransplantation, member Wissenschaftlicher Beirat Deutsche Krebshilfe Dr. Mildred Scheel-Stiftung für Krebsforschung, member
1987-	Arbeitsgruppe "Organtransplantation" der Deutschen Bischofskonferenz, member
1984-88	Arbeitsgemeinschaft der Transplantationszentren in der Bundesrepublik Deutschland einschl. Berlin-West, founder and chairman
1988-	Chirurgische Arbeitsgemeinschaft der Transplantationschirurgie (CAT) der Deutschen Gesellschaft für Chirurgie, Chairman Fachgutachter für das Fachgebiet Chirurgie der Deutschen Forschungsgemeinschaft, referee
1989-	Vorstand Kuratorium der ERNST JUNG-Stiftung für Wissenschaft und Forschung, Chairman Collegium Philosophicum des "Forschungsinstitutes für Philosophie Hannover", Member

PUBLICATIONS

Total: approximately 400 as author or coauthor
Main topics: abdominal surgery, organ transplantation, immunology, ethical issues in surgery

MAIN AREAS OF INTEREST AND RESPONSIBILITY

Surgical oncology, in particular gastric, hepatic and colon surgery, liver surgery: kidney transplantation (from 1968), liver transplantation (from 1972), general areas of transplantation medicine

AN OVERVIEW OF THE EVOLUTION OF TRANSPLANTATION: A PERSONAL EXPERIENCE

Raffaello Cortesini

Address: 2nd Department of Surgery
University of Rome
"La Sapienza" Medical School
Rome, 00161 Italy

1963

Raffaello Cortesini

1990

AN OVERVIEW OF THE EVOLUTION OF TRANSPLANTATION: A PERSONAL EXPERIENCE

Raffaello Cortesini

Early Experiences: The Kidney Transplant

In the 1960s (1960-1962), three very important events occurred at the Harvard Surgical Laboratories in Boston: Dr. Roy Y. Calne arrived from England with a Harkness Fellowship of the Commonwealth Fund. After a series of kidney homografts on dogs, Dr. Calne succeeded in achieving a long-term survival (47 days) maintained on 6-mercaptopurine. His 1960 report in Lancet ends with this statement: "My observation with 6-mercaptopurine suggests that drug can modify the rejection of renal homografts in dogs. It could have advantages over total body irradiation in being less hazardous, and possibly less crippling immunologically, though it seems to increase liability to infection and cause hepatic biliary stasis...Its use might thus offer an approach for renal homografting in man, especially in chronic uremic patients in whom homograft rejection is already depressed" (1). The first event then was the discovery that drug immunosuppression was superior and more applicable than whole-body irradiation.

Secondly, the bilaterally nephrectomized dog with a homotransplanted kidney in the lower abdomen became the standard animal model for kidney transplantation research. This technique was established by Dr. Murray. Thirdly, 6-mercaptopurine was made readily available by the Borroughs Wellcome Pharmaceuticals and the important collaboration of Dr. Hitchings. The result of this "summit" of three important scientists (Drs. Murray, Calne, and Hitchings) marked the sudden burst of advanced activity in this field and opened the way for extensive clinical application of kidney transplantation.

I arrived in Boston in August 1962, with a Fullbright Fellowship just in time to work at the Harvard Surgical Laboratories with Dr. Guy Alexandre from Belgium. He showed me the technique for performing kidney transplantation in dogs. I observed the transplant performed in a patient who survived more than one year. This patient was treated with a by-product of 6-mercaptopurine - synthesized in the Borroughs Wellcome Research Laboratories in Tuckakoe, New York by George Hitchings - called azathioprine, a drug found to be less toxic than 6-mercaptopurine that could be given orally, rather than by injection. In the experimental laboratory we also used azaserine, actinomycin C, and prednisone to find a better mixture of immunosuppressive drugs. Kidney graft survival continued in some of the animals after the drugs had been stopped, raising hopes that it might be possible to discontinue drugs in patients with prolonged transplantation success (2).

That same year, I spent a training period with Dr. W.J. Kolff in Cleveland, learning how to use his artificial kidney machine, the twin coil. After that, I tried to meet Tom Starzl in Chicago because I was interested in his liver transplantation experiments. Unfortunately, he was in Denver. Finally, in October 1962, I returned to Rome with exciting, ambitious plans to develop a transplantation program. Simultaneously starting in the Spring of 1963, kidney transplantation programs using drugs as immunosuppression expanded very rapidly indeed: at the Brigham Hospital in Boston, in Richmond, Virginia, Denver, Paris, London, and Edinburgh, Scotland. In June 1963, I visited Roy Y. Calne at Westminster Hospital in London, where he was performing only cadaver kidney transplants. At that time, two of eight transplanted patients were still living, but only one had good function. Shortly thereafter, I went to Edinburgh to attend a short transplantation course organized by Professor Woodruff with lectures in basic immunology, transplantation immunology, and clinical transplantation. I was the only participant from outside the United Kingdom. I was very impressed by the experimental and clinical work performed by Professor Woodruff and his team. They reported on 11 living-related donor kidney transplant patients, five of whom were doing well (two were identical twins). More data concerning the work done in this field by different groups were available by late 1963, especially from the Denver team led by Drs. Thomas Starzl and William A. Waddell. They reported on 46 patients, 29 of whom had good kidney function for at least three months. In addition, they pointed out the possibility of reversing the rejection crisis with augmented steroid doses (150 to 400 mg/day, adding actinomycin C in two to three doses). The most important result of this experience was the demonstration that rejection is not an all-or-nothing phenomenon in clinical kidney transplantation, as was suggested by the experimental research of Calne, Murray, Goodwin, and Hume (3).

In the same year, David Hume reported the experience of the Richmond transplantation team at the American Surgical Association in Phoenix, Arizona. He treated four patients with total body irradiation followed by prednisone and Imuran and used local irradiation of the transplant with 150 rads in two cases, as suggested by W.J. Dempster (4). This technique was subsequently employed at many centers, including ours, for many years. A few months later, I visited David Hume at the Medical College of Virginia in Richmond and I was very impressed by his tremendous energy and creativity. He was carrying on a transplantation program in both experimental and clinical fields. His observations were remarkably clear and his immunobiological and immunosuppressive research was definitive proof of the importance of the new immunosuppressive drug approach in transplantation. In 1963, I started a broad experimental transplantation program in Rome, performing kidney transplants in bilaterally nephrectomized dogs and testing different dosages of Imuran, actinomycin C, azaserine, methotrexate, and prednisone (5). During 1964, I visited W. J. Kolff and S. Nakamoto at the Cleveland Clinic where they were performing kidney transplants with encouraging results. I then visited Tom Starzl in Denver. He was working feverishly in the experimental lab, helped by Tom Marchioro, performing two liver transplants a day in dogs, kidney transplants in humans, and finally, writing *Experience in Renal Transplantation*, which was practically finished and almost ready for the publisher. This was the first textbook on renal transplantation, a peerless source of experiences and data based on the 64 cases accumulated by that time at the University of Colorado. From March 16, 1962, through March 15, 1964, 290 patients, worldwide, received kidney transplants, and 114 survived with a functioning graft for the first posttransplant year. F. D. Moore started talking about a "cautious optimism" in the field of transplantation. With this impetus given to renal transplantation from 1962 to 1964, a startling proliferation of transplant centers appeared in the United States and Europe. Renal transplantation was transferred from the laboratory to the hospital. Doctors in all these hospitals were seeking to establish a new, safe, practical, and effective routine. There was a growing belief that it would be possible to obtain long-term survival in a patient by maintaining him in good health with a transplanted kidney in place, his own diseased kidney removed, and immunosuppression by means of drugs.

Xenografts from Primates

One of the limiting factors in the treatment of irreversible renal failure by kidney transplantation is the shortage of suitable human kidneys (as written in the British Medical Journal, January 1965). The use of living donors raises serious ethical problems according to Professor Woodruff's article in the same Journal (1964, 1:1457), while cadaver kidneys, even those free from disease, are sometimes found to have sustained serious agonal or postmortem damage. If animal kidneys instead of human kidneys could be transplanted into man, the problem of obtaining transplants could be reduced simply to that of breeding sufficient healthy animals of the right species, concluded BMJ in the same article.

This was the project I started in December 1963 when I noticed in the December 27, 1963 issue of Time magazine an article entitled "Spare Parts from Chimp to Man." The article concerned patient Davis and surgeon Reemtsma. I was impressed by the fact that the two kidneys of an 80-pound, seven-year-old chimpanzee functioned for more than two months in a 44-year-old Black dock worker, kept alive with peritoneal dialysis for chronic renal insufficiency. A month and a half after his operation, Davis strode into a Tulane news conference and proclaimed: "I feel better now than I have in five years." How did he feel about having kidneys from a chimpanzee? "The doctors explained I couldn't live with what I'd got. I was worried, of course - but not about the animal business. I knew it would be a monkey. It didn't bother me. All I wanted was to survive. I feel wonderful." The 12-man team of physicians and surgeons, headed by Dr. Keith Reemtsma, emphasized that the Davis transplant was no science-fiction spectacular. Said Dr. Reemtsma: "We have taken every precaution with this transplant. Even if it should now fail, we could still defend its use ethically and medically."

In the same month, December 1963, the famed Denver transplant team headed by Tom Starzl put a baboon's kidney in the flank of a 40-year-old man. His condition after the transplant: "Satisfactory." In February 1964, I went to Denver and then to New Orleans. I had an in-depth discussion with Keith Reemtsma about the problems of heterotransplantation. In those years we did not use the term xenotransplantation, but we adopted the name heterotransplantation as a graft between two animals of different species. From that time, Keith Reemtsma and I became very close friends, and I consider him an extraordinary man, one of the outstanding pioneers in transplantation. I saw the patients transplanted, the technique to transplant en bloc the two chimp's kidneys, the immunosuppressive protocol, and the follow-up of renal function. I also had an extensive and helpful discussion with Charles De Witt, the pathologist charged with studying how to select the donors. Chimpanzees and man share the same major ABO groups: 10 to 15 percent are type O, the others are type A. After a short visit to David Hume in Richmond, I went back to Rome, firmly believing that sooner or later, heterotransplantation would be a reality. In August 1964, I received a letter from Keith. I want to relate some paragraphs:

"Things are moving along here, and I wanted to keep you informed on our work. We've accumulated much more data, and I'll try to give you a summary. First of all, the patient you saw here, the young woman who received a renal heterotransplant in January, continues to do well. She has normal renal function now almost seven months after transplantation, and she is on 75 mg Imuran and 25 mg prednisone daily. She is out of hospital and asymptomatic. She was getting a bit hyperglycemic, but this returned to normal as the steroids were reduced. Her most recent values, yesterday, were as follows: BUN 17, serum creatinine 1.0; creatinine clearance 105;

fasting blood sugar 130 and WBC 6,000. Enclosed is a summary of the data on this patient.

Another item of interest is the immunologic study of cytotoxicity. Dr. De Witt now believes that it is a more accurate index of rejection than the hemagglutination titers that we discussed when you were here. If you'd be interested in the details of these studies, I'd be happy to ask Dr. De Witt to send them along. We are very interested in studying blood of groups of chimpanzees, and I wonder if I might ask a favor. We would like to get blood samples from the chimpanzees in your colony, particularly from animals that might be available for trade or purchase. We would be happy to send the equipment, containers, instructions, and shipping cartons, so that I don't believe it would be too much trouble at your end. Doctor De Witt would do all the hematologic studies, without charge, of course, and we would send you back the results of all the tests. This might be of help to you, and it would help us in having a wider experience in hematologic studies of chimpanzees.

There are many details which I hope I can discuss with you before too long. In the meantime, if there is any specific information I can send to you, or if I can help in your program in any way, just let me know."

At our center during 1965, we studied all the chimpanzees of the Rome Zoological Garden. We studied more than 25 chimps and we learned how to anesthetize the animals. We employed a powerful tranquilizer, Sernyl, to take blood samples. We checked all the humoral parameters, including renal and hepatic function, the immunoglobulins, and the blood groups. We had great cooperation from Professor Brunetto Chiarelli, a famed primatologist from the University of Turin, and from Professor J. Moor-Jankoswky from the New York University School of Medicine, New York.

In the first months of 1966 we imported three big chimpanzees from a German zoological garden. These animals were carefully studied. Creatinine clearances were 78, 98, and 78 ml/min/m^2, respectively. Clinical and laboratory examinations revealed entirely normal animals. In April 1966, a 19-year-old patient was admitted to our institute with the diagnosis of chronic glomerulonephritis and uremic coma.

He was placed on hemodialysis, but in a few weeks he demonstrated a slow deterioration of hepatic and cardiac functions. No living or cadaver donor was available, so we decided to perform a kidney heterotransplantation from one of the three chimpanzees already studied in our Laboratory. The one we selected was 20 years old, weighed 52 kg, and was blood type A, the same as the recipient. Urographic and aortographic examinations revealed normal patterns: bilaterally only one renal artery and one renal vein. The final decision was to transplant only the left kidney to preserve the life of the donor. Professor Paride Stefanini, Chairman of the department, and I performed the transplant. Carlo Casciani joined us, taking care of the medical aspects. The left kidney was removed through a transabdominal approach with a xifopubic incision. The organ was then perfused by an electrolytically balanced hyperosmotic solution, first with 200 ml at 20°C and then with 150 ml at 6°C, in order to induce a progressive cooling of the kidney. The kidney was put into the right iliac fossa of the patient, who previously had a bilateral nephrectomy. The urinary output was 2100 ml in the first 24 hours and subsequently decreased to 1100-1650 ml/24 hours. Renal function was always satisfactory. Antirejection therapy included azathioprine, prednisolone, and actinomycin C. The first two-week postoperative period was absolutely normal. After that, the patient showed a perforated duodenal ulcer that was surgically repaired. Subsequently, the patient developed a peritonitis and died on the 30th postoperative day. There was no evidence of rejection at any time during the postoperative period. The kidney did not show histologic abnormalities; there was no interstitial or perivascular infiltrate, a few glomeruli presented a slight thickening of basal membrane. The donor survived more than two years in our laboratory (6).

A great discussion followed our operation: many in favor, some strongly against. I continued the research in this field with Brunetto Chiarelli, and from 1967 to 1970, our in-depth studies included the comparative genetics in primates, the immunoelectrophoresis of protein serum, and the possibility of breeding chimpanzees. In December 1969, I attended an international symposium on infections and immunosuppression in subhuman primates in Rijswijk (organized by WHO and Radiobiological Institute TNO, Holland) presenting the current state of heterotransplantation (7). Hans Balner, who defined the chimpanzee leukocyte antigens and used chimpanzee isoantisera for leukocyte typing in man in 1967 (8), was present at that meeting. We were already very close friends and shared the same interest for future developments in xenografting.

Subsequently, I began a series of experiments on long-term hepatic support employing a baboon liver as an extracorporeal organ to support recovery of the primary liver in human fulminant hepatitis cases. In November 1972, we successfully treated a case of hepatic coma with a liver assist device combining a hemodialyzer and an isolated baboon liver connected with the patient's circulation. After 15 hours the patient became fully conscious with gradually improving biochemical and clinical parameters; over the first week, we noted a gradual and continuous liver regeneration. The patient recovered perfectly (9). I will end this story with a brief comment: In 1963, Keith Reemtsma stimulated us in a new field, the importance of which will assume a greater significance in the future. I am convinced that animal transplantation in this decade will become a real possibility because, as Tom Starzl said, of how close efforts at both chimpanzee-to-human and baboon-to-human transplantation came to succeeding in that now distant time (10).

Living Donors

Ethical problems in transplantation have existed since clinical applications began. There are, of course, certain limitations on which organs can be obtained from living donors; for example, no one can donate a heart or an entire liver and remain alive, nor can one donate a kidney if it is the only one functioning. But what about the person who wants to donate one of two healthy kidneys? In 1966, Professor M.F.A. Woodruff felt such donations are justifiable if certain conditions are met: most importantly, that donation is genuinely voluntary, and that the donor is aware of the risk he is accepting and the chance that his sacrifice may not benefit the patient (11). This argument was one of the many ethical and legal issues addressed at the Ciba Foundation Symposium held in London from March 9-11, 1966 and promoted by Sir Michael Woodruff. A small group of scientists, lawyers, theologians, and others concerned with the ethical and legal problems of organ transplantation participated enthusiastically in the discussion chaired by the perceptive and sympathetic Lord Kilbrandom. In the final discussion, J.P. Revillard outlined the conditions that would permit the removal of a kidney from a living donor: pressures on the donor must be completely absent, advantages to the recipient must always outweigh the disadvantages or danger to the donor, direct payment must not be accepted, and the social security system or the public health service should insure the donor's life. Professor Doube refused to support kidney donation from prisoners because he felt that a person under restraint cannot be presumed to consent. The con-

Ciba Foundation Symposium, 1966

R. Cortesini M.L. Revillard J.P. Revillard

Second Department of Surgery, University of Rome, 1968

C.N. Barnard B. Baroni R. Cortesini P. Stefanini clusions of this conference had great influence on the field of living donation and are still widely accepted. I proposed a law concerning living-donor kidney transplantation to the Italian Parliament. The law was approved in June 1967, making it the first national law of its kind (12). I had the support of several Catholic theologians, such as Cardinal Aurelio Sabattani who wrote in 1965: "In brevis eiusdem ordinis, licite proefertur bonum proximi." The principle of the "charitas erga proximum," inspires the Catholic ethics of living-donor tissue and organ donation (13).

Cerebral Death

Since ancient times, it has been apparent that death occurs upon the cessation of respiratory and cardiac function. The respiratory and cardiac resuscitation devices developed in the middle of this century could often restore the function of the heart and lungs but might leave more sensitive organs like the brain irreversibly damaged; this left us with serious moral, ethical, psychological, religious, and legal ramifications. The transition from a cardiac-based to a cerebral-based definition of death was a major ordeal that deeply involved many transplant surgeons. A large number of meetings, symposia, conferences, and informal discussions were held, with physicians, clergy, and other intellectuals interested in the phenomena of death participating. I have been involved with the issue of brain death from the beginning. At the Ciba Foundation Symposium in March 1966, I remember G. P. J. Alexandre affirming: "I would like to tell you what we consider as death when we have potential donors who have severe chronic cerebral injuries. In nine cases we have used patients with head injuries, whose hearts had not stopped, to do kidney transplantation. Five conditions were always met in these nine cases: 1) complete bilateral mydriasis; 2) complete absence of reflexes, both natural and in response to profound pain; 3) complete absence of spontaneous respiration five minutes after mechanical respiration has been stopped; 4) falling blood pressure, necessitating increasing amounts of vasopressive drugs, either adrenaline or Neo-synephrine; 5) a flat EEG. All five conditions must be met before the removal of a kidney can be considered." Joseph Murray considered those criteria excellent and added: "This is the kind of formulation that we will need before we can approach the legal profession." Tom Starzl had some doubts: "I wonder if any of the members of our transplantation team could accept a person as being dead as long as there was a heart beat. We have been discussing this practice in relation to renal homografts. Here, a mistake in evaluation of the 'living cadaver' might not necessarily lead to an avoidable death since one kidney could be left. But what if the liver or heart were removed? Would any physician be willing to remove an unimpaired vital organ before circulation had stopped?" J. P. Revillard, Sir Michael Woodruff, Roy Calne, Reverend Canon Bentley, George Shreiner, and Jean Hamburger discussed with great interest the new definition of death, but many doubts remained. Roy Calne concluded: "I feel that if a patient has a heart beat, he cannot be regarded as a cadaver. Any modification of the means of diagnosing death to facilitate transplantation will cause the whole procedure to fall into disrepute with the rest of the profession."

On March 16, 1966, we left London with the impression that the first step had been taken in the direction of a better and more precise definition of death to be applied in the transplantation field, but no one could have predicted that on December 3, 1967 at the Groote Schuur Hospital in Capetown, Chris Barnard would perform the first human heart transplant from a heart-beating donor! Since then, the concept of cerebral death was the main item of every discussion. The original Harvard criteria discussing the concept of brain death under the rubric of "irreversible coma" were set forth in 1968. In the same year, the Declaration of Sydney added two important statements to the diagnosis of brain death in relation to organ transplantation. The first was a reaffirmation that death is a process, and although a large mass of cells in a multicellular organism might be alive, the organism as a whole could still be considered dead; the second declared that in situations related to organ transplantation, the pronouncement of death should require two physicians unrelated to the transplant procedure itself. In the following years I worked at the international level to firmly establish the criteria to determine the exact moment of death. I remember the Council for International Organizations of Medical Sciences (CIOMS) in Paris in 1967 and Geneva in 1968. Also in 1968, the Italian Ministry of Health issued a decree concerning all the formalities to follow for the determination of death, but when I removed a kidney from a heart-beating donor in January 1970, the public prosecutor of Rome accused me of homicide! Two years of debate were required to establish that the donor was really a cadaver.

Finally, the Italian Parliament approved a law defining the determination of brain death for organ transplantation purposes in 1975.

Liver Transplantation

The first human-to-human liver transplantation was performed by Tom Starzl on March 1, 1963. This first recipient died of hemorrhage during the conclusion of the operation. The second and third liver homotransplant recipients lived for 22 and 75 days, respectively, both ultimately dying from multiple pulmonary emboli (14).

I visited Denver for the first time in February 1964, before going to work with Keith Reemtsma in New Orleans. I learned how to perform liver transplants in dogs at the small experimental laboratory near the Veterans Administration Hospital. I spent the following years in Rome, studying the various problems in liver transplantation. Our experience in kidney transplantation provided limited help, but the liver is a far more complicated organ, and its derangement leads to vastly more complex physiologic impairments. We learned that both immunosuppression and liver preservation are very important, and that the recipient will be lost if the transplanted liver does not function efficiently from the moment of anastomosis.

The problems in liver transplantation were technical and immunological, concerning both preservation and immunosuppression: In February 1965, Tom Starzl presented a paper at the 26th Annual Meeting of the Society of University Surgeons in Philadelphia in which he outlined the determinants of short- and long-term survival after orthotopic liver homotransplantation in dogs. In this paper he states: "The present canine studies provide increased hope that orthotopic hepatic homotransplantation may ultimately have use in the treatment of human liver disease." At the same meeting, Francis D. Moore said: "I think this work of Dr. Starzl and his coworkers is the most exciting work in the transplant field since the initial reports by Calne, and later by Zukoski, Murray, and Alexandre, showing the maintenance of intact renal histology with immunosuppression. Now, after a few years and a lot of work, we are beginning to get to the same place with the liver. Dr. Starzl and his team have furthermore shown a classic thing about transplant research in general. Namely, that they have made an experimental plan, have perfected their own operative procedure, and then have stuck to it, running through a good series of animals with good controls and a careful effort to compare various immunosuppressive regimens."

I was also very impressed by these studies and performed hundreds of liver transplants in dogs and pigs (15) from 1965 to 1970. In December 1968, I invited Tom

Starzl to the second Congress of the Italian Society of Organ Transplantation in San Remo. He summarized the clinical results obtained at that time: "There have been a series of futile attempts of orthotopic transplantation until the summer of 1967, and they were futile in the sense that two of the patients - two of the series of nine - at our place, Boston, and in Paris, died as a consequence of the operation; the others all died between six and 23 days after operation...There were 14 patients in all treated from July 1967 to five months ago, until July 1968. Three of these patients died as the immediate cause of operation, and in all cases there was a vascular accident and the artery clotted or the portal vein clotted. Of the other 11, there was one who lived for 13+ months and then died of carcinomatosis. There are five more who are living now, after 10-and-a-half, nine-and-a-half, eight, and seven months. The other six children - those who died after having survived the operation - died after 35 days, 105 days, 135 days, and 186 days. Those are the survival statistics." These results demonstrated that liver transplantation was a feasible and legitimate, albeit at that time imperfect, form of treatment. In these years, Tom Starzl stated many times that liver transplantation may be considered as a last best hope in certain cases. In September 1970, when his longest-surviving patient had exceeded two-and-a-half years posttransplant survival, he wrote: "With more experience, with successful efforts to reduce the toxicity of immunosuppressive agents, with improvements in histocompatibility typing, and with advances in preservation and storage techniques, the record can be expected to improve" (16). Today liver transplantation is a widely accepted therapeutic treatment. Many transplant surgeons have contributed to this success, but Tom Starzl, with his perseverance, creativeness, and extraordinary will power, has been the real pioneer in this field.

Artificial Heart and Cardiac Transplantation

The heart was clearly the jackpot of transplantation surgery, and in the early 1960s, many American surgeons moved to claim success. At Stanford University, Dr. Norman Shumway and Dr. Richard Lower began a series of heart transplants in dogs, refining the surgical technique that would later become the basis for all heart transplantations. At the University of Mississippi, Dr. Hardy moved toward his historic chimpanzee heart-into-man operation in 1963. At the same time in Houston, Michael De Bakey chose to concentrate on a heart that would not be wrapped in legal, moral, and religious issues: His heart would be plastic and metal - an artificial heart. Others had the same goal; Willem Kolff, the pioneer of the artificial kidney worked on a different type of artificial heart. The first artificial heart design of this group was an electromagnetic heart implanted into a dog in January 1959. In August 1962, I visited his laboratory in Cleveland and met Tetsuzo Akutsu, who was building a pneumatically driven silastic sac heart. The housing of this heart was rigid. During diastole, the blood sac was filled with blood when distended to the walls inside the housing; during systole, it was compressed, and the blood mass was ejected into both great vessels: the aorta and the pulmonary artery. This basic system was gradually improved, and during this visit, Akutsu could report that the first animal in the world had lived longer than 24 hours with this type of artificial heart (17). In 1966 after further tedious work, Kolff and Nose could report a two-day survival. Kolff then moved to Salt Lake City, Utah, and with the cooperation of Kwan-Gett in 1970, obtained one-week survival with a new model of artificial heart (18). In 1971, Akutsu and Kolff working independently in Jackson, Mississippi and in Salt Lake City, respectively, obtained greater than 10-day survival in calves with artificial hearts. At that time in the heart transplantation field, many significant events occurred. On December 3, 1967, a bulletin flashed across the world from Groote Schuur Hospital in Cape Town South Africa: "The first human-to-human transplant in history was done last night by a team of doctors at Groote Schuur Hospital. The name of the patient, as well as the donor, is being withheld by hospital authorities. The heart transplant team was led by Professor Christiaan Barnard in a dramatic all-night operation - the first of its kind in medical history."

Three days after Barnard transplanted a heart into Louis Washkansky, Dr. Adrian Kantrowitz became the first American surgeon to attempt the procedure and fail. He installed a new heart into a newborn child, but the infant died six-and-a-half hours posttransplant in Brooklyn's Maimonides Hospital. A month later at Stanford Medical Center, Dr. Norman Shumway attempted his first heart transplant, but the recipient died 15 days posttransplant. Shumway's near decade of intense research in transplantation and the knowledge obtained from transplanting hundreds of animal hearts had made him the preeminent figure in the field. In his book *Hearts*, T. Thompson wrote that it was ironic that if Shumway had been the first, then the medical world would have said, "Of course Shumway did it. He was eminently qualified to do it. He has done more research on the procedure than any man in the world and we have read his papers and heard his speeches and if any man try it, then Shumway is he..."

But, unexpectedly, Christiaan Barnard was first - unexpected because few had even heard of Christiaan Barnard and because the world was not accustomed to dramatic breakthroughs occurring in South Africa. If a heart transplant could be done by an obscure surgeon at the bottom of the world, then it must not be especially difficult. Furthermore, Barnard was blessed with excellent success: Although his first transplant lived only 18 days, his second, the dentist Philip Blaiberg, survived for several months (20). I had the opportunity to speak with Norman Shumway during a Congress of the International Society in Wien in September 1967. He was afraid to start clinical heart transplantation, stating: "If I take a beating heart from a human donor in California, I would be prosecuted!"

So Christiaan Barnard opened the door of heart transplantation in man. He came to Rome in January 1968 and spoke with me at length. Since that time, I invited him to all the international symposia on heart substitution in Rome from 1973 until 1982. Chris always defended his operation; a few months later, after his first visit he wrote: "These operations, as might be expected, met with reactions ranging from acclaim to condemnation. Of the various criticisms one above all others merits the most careful consideration: the objection that heart transplantation in man in premature. To refute this criticism, three basic questions need to be considered. First, is there any need of this type of surgery - have we patients who can benefit by this new technique? Second, have we developed this technique sufficiently to use it without undue risk in the treatment of human beings? Third, are we able to detect the implications that may follow this type of procedure, and can we effectively control them when they arise? I should like to answer these questions in the light of our experience with the first two human heart transplantations we have performed." After carefully presenting the patients' clinical courses, the surgical technique, and the immunosuppressive treatment, Barnard concluded: "We have shown this operation of human heart transplantation to be eminently feasible, and in these two cases it carried no direct surgical mortality. We are also able to detect and treat possible complications with a high incidence of success, but it is clear that here still lie the major risks and challenges to enduring success. The World Medical Association has decided that the use of tis-

Heart
Foundation
Meeting,
1968

R. Cortesini

Father Boulogne
first heart transplant in France

Seventh Congress
of The Transplant
Society,
Rome, 1978

First General
Audience of
Pope John Paul I,
September 1978

sues and organs for transplantation should be governed by certain rules. Among the suggestions they have made are the following: in the treatment of a sick person, the physician must be free to use the new therapeutic measure if, in his judgment, it offers hope of saving life, restoring health, or alleviating suffering. I think we alleviated the suffering of our first patient although we did not save his life. It is not quite certain yet for how long we have saved the second patient's life, but I have no doubt that we have alleviated his suffering. In conclusion, I believe that we have dealt with all three questions relating to whether clinical cardiac transplantation in the human is premature. Final judgment of this issue will rest with a growing number of gravely ill patients who are salvaged, and with the testimony of time" (20). In July 1973, I organized a meeting in Fiuggi (near Rome) to discuss the problems of heart transplantations and artificial hearts. I was implanting the Kwan-Gett artificial heart in calves and was convinced that the limited supply of heart donors could be solved with the development of a reliable artificial device. Barnard, Dubost, Akutsu, Graham, and others were present, and it was concluded that "heart transplantation needs more basic biological research; artificial hearts with an external power source are not too far from clinical trials, and for an all-inside system, we will probably have to wait longer" (21).

We had other meetings on heart substitution in Fiuggi or Rome: in June 1975, September 1978 during the Seventh International Congress of the Transplantation Society, and May 1982 (22).

On December 2, 1982, the first permanent totally artificial heart was implanted into a patient at the University of Utah by a team headed by W.J. Kolff. Despite continued excellent function of the totally artificial heart, the patient succumbed after 112 days to vascular collapse secondary to septicemia. The totally artificial heart was subsequently employed as a temporary device while the patient awaited a suitable donor heart (23,24). Human heart transplantation and the artificial heart became a reality, thanks to the combined efforts of surgeons and bioengineers and through a continuous international exchange of information and ideas. It is impossible in this short note to remember all the courageous and persevering people involved. All deserve our admiration and credit.

CONCLUSIONS

In my 29 years of experience, the most fascinating aspect was the network of people involved in transplantation. With most of them I share a close, personal friendship and I consider them to be extraordinary individuals. I must first mention Felix Rapaport, a great scientist, a marvelous personality, and one of my closest friends. He devoted his entire life to transplantation, both organizing the Transplantation Society and editing *Transplantation Proceedings* - the bible of transplantation. I shared many years of cooperation with all the tissue typers, firstly with Ruggero Ceppellini, and with Hans Balner, Jean Dausset, Jon van Rood, and Paul Terasaki. Their contribution to transplantation medicine has been tremendous, even if they have often been misunderstood by the surgeons. The discussions have always been very lively, as at the Third International Transplantation Society Congress in Holland in September 1970, when the lack of correlation between HLA matching and the result of cadaver donor transplants demonstrated by Paul Terasaki sent tissue typers and surgeons on divergent courses for the next 20 years. I followed the tissue typers very closely, admiring how they elucidated the HLA system, and participated in the Histocompatibility Workshop. Their discoveries paved the way for the knowledge of human genoma and its molecular mechanisms. The future implications of these studies are absolutely unfathomable.

On the other side of the coin were the transplant surgeons, a very peculiar breed. All were very aggressive, fearless, resourceful, highly trained both experimentally and clinically, able to work 18-20 hours a day, moving night and day by car or by plane to harvest organs, always surrounded by residents, students, transplant coordinators, scrub nurses, laboratory technicians...

In transplantation, the success often was due to the teamwork of so many anonymous persons. They were involved in making organ transplantation - kidney, liver, heart, lung, and pancreas - a major clinical reality. They devoted time, energy, and enthusiasm to this enterprise and deserve our gratitude. The future will bring many new horizons, but never again will immunologists and surgeons work so closely as they did in this chapter of the great adventure of transplantation. It was an exciting and productive time which everyone involved can remember with nostalgia.

REFERENCES

1. Calne RY. The rejection of renal homografts inhibition in dogs by 6-mercaptopurine. Lancet 1960; 1:417.
2. Murray JE, Merrill JP, Dammin GJ, et al. Kidney transplantation in modified recipients. Ann Surg 1962; 156:337.
3. Starzl TE, Marchioro TL, Waddell WR. The reversal of rejection in human renal homografts with subsequent development of homograft tolerance. Surg Gynecol Obstet 1963; 117:385.
4. Hume DM, Magee JH, Kauffman MH, et al. Renal homotransplantation in man in modified recipients. Ann Surg 1963; 158:608.
5. Cortesini R, Casciani C, Arullani A, et al. Il trapianto renale sperimentale. Il Policlinico Sez Chir 1964; 71:417.
6. Cortesini R. Discussion of paper by Reemtsma K. Renal heterotransplantation. In: Transplantation von Organen und Geweben. Seiffert KE, Geissendorfer R, Eds. Stuttgart: Georg Thieme Verlag, 1967; 153.
7. Cortesini R, Casciani C, Cucchiara G. Heterotransplantation in primates: Current state of affairs. In: Proceedings of the International Symposium on Infections and Immunosuppression in Subhuman Primates. Balner H, Beweridge J, Eds. Munksgaard, Copenhagen, 1970; 239.
8. Balner HA, Van Leeuwen H, Dersjant H, et al. Defined leukocyte antigens in chimpanzees: Use of chimpanzees isoantisera for leukocyte typing in man. Transplantation 1967; 5:664.
9. Cortesini R, Vellucci A, Cucchiara G, et al. Bio-artificial liver: A combined system of hemodialysis and baboon liver perfusion. Trans Am Soc Artif Int Organs 1973; 19:365.
10. Starzl TE. Baboon renal and chimpanzee liver heterotransplantation. In: Xenograft 25. Hardy MA, Ed. Elsevier, 1989; 17.
11. Woodruff MFA. Transplantation: the clinical problem. In: Ethics in Medical Progress. Wolstenholme GEW, O'Connor M, Eds. Churchill, London, 1966; 10.
12. Cortesini R. Outlines of a legislation on transplantation. In: Ethics in Medical Progress. Wolstenholme GEW, O'Connor M, Eds. Churchill, London, 1966; 171.
13. Sabattani A. Aspetti morali e giuridici dei trapianti di organo. Minerva Med 1965; 56:543.
14. Starzl TE, Marchioro TL, Von Kaulla KN, et al. Homotransplantation of the liver in humans. Surg Gynecol Obstet 1963; 117:659.
15. Cortesini R, Arullani A, Casciani C, Baroni B. Il trapianto ortotopico di fegato sperimentale. Il Policlinico Sez Chir 1968; 6:1.

16. Starzl TE, Giles G, Lilly JR, et al. Indications for orthotopic liver transplantation: with particular reference to hepatomas, biliary atresia, cirrhosis, Wilson's disease, and serum hepatitis. Transplant Proc 1971; 3:308.

17. Akutsu T, Mirkovitsch V, Topaz SR, et al. A sac type of artificial heart inside the chest of dogs. J Thorac Cardiovasc Surg 1964; 47:512.

18. Kwan-Gett CS, Bachman DK, Donovan FM, et al. Artificial heart with hemispherical ventricles II and disseminated intravascular coagulation. Trans Amer Soc Artif Intern Organs 1971; 17:474.

19. Thompson T. Hearts. Fawcett, Greenwich, Conn, 1971; 162.

20. Barnard CN. Human cardiac transplantation: an evaluation of the first two operations performed at the Groote Schuur Hospital, Cape Town. Am J Cardiol 1968; 22:584.

21. Panel discussion on heart transplantation or artificial heart? In: International Symposium on Heart Substitution. Cortesini R, Ed. Transplant Proc 1974; 6.

22. Cortesini R, Ed. Third International Symposium on Heart Substitution. Transplant Proc 1984; 16:877.

23. Cortesini R, Cucchiara G. Total artificial heart replacement with consecutive heart transplantation. In: Assisted Circulation. Unger F, Ed. Springer-Verlag, Berlin, Heidelberg, 1979; 388.

24. Miller CA, Pae WE, Pierce WS. Combined Registry for the clinical use of mechanical ventricular assist pumps and the total artificial heart in conjunction with heart transplantation: Fourth Official Report 1989. J Heart Transplant 1990; 9:453.

CURRICULUM VITAE

Raffaello Cortesini

PERSONAL

Born: November 3, 1931; Milano, Italy

Address: 2nd Department of Surgery
University of Rome
"La Sapienze" Medical School
Rome, 00161 Italy

EDUCATION

1950-56	University of Rome "La Sapienza" Medical School
1956-61	University of Rome "La Sapienza" Post-graduate Medical School in General Surgery

POSITIONS

1956-60	Clinical and surgical training in cardio-thoracic surgery University of Rome
1960-61	Training in general surgery, St. John Hospital of Rome
1962	Fullbright Fellowship, the Baylor University Medical School, Houston and Peter Bent Brigham Hospital, Boston
1963-66	Assistant Professor of Surgery, University of Rome
1966-71	Chief, Transplant Service, 2nd Department of Surgery University of Rome
1968-71	Director of Institute for Organ Transplantation, National Research Council
1971-79	Professor of Experimental Surgery, University of Rome Medical School
1971-89	Director, Transplantation Service, University of Rome Medical School
1979-	Professor of Surgery, University of Rome Medical School
1989-	Chairman, 2nd Department of Surgery, University of Rome, Medical School
1989-	Director, Italian Consortium for Organ Transplantation

PROFESSIONAL SOCIETIES

International Transplantation Society
International Society of Surgery
International Society for Heart Transplantation
American Society for Artificial Internal Organs
European Society for Organ Transplantation
European Society for Artificial Organs
Societe Francaise de Transplantation
Societa Italiana dei Trapianti d'Organo

PUBLICATIONS

Total: 400

INDEX

Abouna G
278
Accetta D
327
Ackerman JR
49, 166
Adler F
322
Aeger D
233
Aglietta M
426
Aird I
310, 639
Akutsu T
685, 688
Al-Askari S
360-362
Albert E
492, 522,523, 648
Alexandre G
47, 53, 337, 338, 345, 677, 683, 684
Algire G
188, 479
Allen
478
Allen JG
437
Allen SL
29, 477
Allison P
650
Alpen E
397
Alter B
543, 545, 546
Alway R
437
Amacher P
205
Amiel
645
Amos DB
10, 26, 30, 107, 209, 211, 274, 278, 318, 322, 363, 385, 475, 476, 488, 491, 508, 523, 541, 641, 644
Anderson D
124
Anderson N
188
Anichini A
546
Ascher
282
Atkins H
639
Atkins L
315
Attalah
43
Auchincloss H
320, 328
Austen KF
320
Austyn J
653
Auvert J
39, 41, 51
Awasaki Y
487
Ayoub G
525
Bach F
343, 458, 463, 487, 489, 508, 509, 539, 540, 544
Bach M
542
Bahnson H
217
Bailey D
27, 29, 31, 542
Bain B
486, 508
Baines
422
Baker G
320
Baker J
383
Balankura O
219
Baldamus C
327
Balfour H
460
Ballinger
652
Balner H
327, 364, 365, 403, 412, 485, 508, 622, 681, 688
Barber WH
625
Barker C
85, 353
Barnard CN
132, 166, 168, 169, 276, 319, 565, 566, 575, 576, 578, 664, 665, 682, 683, 686, 688
Barnard M
572, 574
Barnes B
320, 321
Barnes D
103
Baroni B
682
Barry J
221
Barth R
29
Batchelor R
107, 208, 364, 622, 623, 645-648, 653
Bauman J
422, 423
Bayer J
422
Beck C
320
Beck G
665
Beck JC
295
Becker
278
Beer A
86
Belzer FO
49, 53, 166, 353, 456, 464, 585, 590, 595, 596
Benacerraf B
24, 29, 136, 318, 327, 368, 645
Benichou J
166
Bentvelzen P
424
Bergan JJ
166
Berrian J
105
Besredka A
619
Bianco M
327
Bigger IA
113
Billingham M
444
Billingham RE
3, 4, 6, 9, 24, 25, 73-75, 95-97, 99-103, 105, 124, 148, 186, 187, 205, 234, 276, 283, 309-313, 317, 325, 352, 360, 364, 478, 513, 618, 622, 663
Binns R
234, 235
Birmingham P
310
Bismuth H
667
Bittner J
203
Bjorkman P
529
Blalock A
147
Bloom W
117
Bodley Scott RV
304
Bodmer J
301, 649

Bodmer W 301, 508, 522, 523, 649, 650
Bol S 422
Bollinger R 654
Bollman JL 167
Boranic M 404
Bordet J 11
Bordley J 382, 383
Borel J 170, 235
Borst H-G 664-666
Bortin M 386, 404, 412, 547
Bosman B 571, 575
Botha MC 575
Bower 273
Boycott B 311
Boyle B 491
Boyse T 10, 107, 322
Bradley R 409, 420
Braf 276
Brandon 251
Bravo-Shugarman M 166, 520
Breedis 84
Brendel W 625, 629, 662-666
Brent L 3, 4, 6, 7, 9, 24, 25, 81, 83, 84, 93, 94, 98, 101, 124, 186, 187, 208, 209, 231, 234, 287, 309-313, 317, 352, 360, 364, 478, 479, 481, 485, 513-515, 591, 618, 622, 629, 648, 653
Brent S 106
Bretscher 545
Brettschneider L 166
Briggs R 83
Bright 229
Brock R 567
Broelsch C 667
Brommer E 424
Brown 251
Brown J 103
Brown JB 124, 136
Bruning H 501
Brynger H 353
Brzytwa A 369
Buckner D 385, 387, 388
Burdette W 209
Burger 574
Burke J 640, 641
Burnet AK 415
Burnet FM 4, 10, 15, 80, 83, 97, 104, 105, 107, 136, 186, 318, 381, 639, 643
Butt K 285, 585, 589, 591
Calne P 131, 232, 650
Calne R 45, 47, 53, 104, 130-132, 138, 147, 151, 154, 158, 164, 166, 169, 170, 192, 209, 227, 228, 232, 236-239, 269, 296, 310, 318, 339, 353, 454, 512, 622, 629, 645, 650-652, 677, 678, 683, 684
Camey M 41, 46
Cannon J 217, 513
Carcassi U 384
Cardozo PL 400
Carlier M 345
Carpenter CB 368
Carrel A 39, 41, 55, 125, 136, 381
Casciani C 680
Casey AE 203, 204
Cass MH 567
Castagnola 422
Castle WE 21
Cavallaro J 327
Caves P 444
Cavins JA 383
Cecka JM 530
Ceppellini R 51, 365, 384, 483, 485, 489, 501, 516, 523, 541, 643, 688
Chandler J 316
Chase C 326, 327
Chase H 80
Chase M 100
Chase RM Jr. 357
Chaver B 459
Chavez-Peon F 327
Cherry M 30, 31
Chia D 533
Chiarelli B 680, 681
Chisholm GD 192
Cho YW 530
Christian H 123
Christian HA 619
Christie RV 304
Churchill ED 310, 314, 318, 617
Cicciarelli J 529
Claman HN 620
Clark B 266
Cleveland RJ 276
Clift R 383, 385, 388
Clot JP 235
Cloudman A 21, 23, 29
Cochrum K 454, 457
Cohen B 664

Cohen C 485

Cohn 545

Cohn R 437, 440, 587, 589

Cole L 397

Colebrook L 79

Collins G 166, 519, 520, 603, 605

Colly L 426

Comfort A 82, 100, 311

Compton C 277

Condie R 165

Congdon C 365, 381, 384, 386, 397

Converse JM 185, 203, 317, 351, 353, 355, 356, 362-369, 485

Conway H 203, 206

Cook D 526

Cooke RA 352

Coons A 617-619, 622

Cooper J 169, 353

Cooper JAD 149

Corry RJ 320, 326

Cortesini R 283, 353, 675, 676, 682, 687

Cosimi AB 165, 320, 324

Couch N 137

Counce S 26, 29

Courtney T 100

Creech O 555

Crick F 6

Cronkite G 384, 426, 427

Crouch W 403

Cruickshank AH 619

Cunha E 205

Curran W 624

Cushing H 591

D'Alessandro A 607, 609

Dallman M 653

Dalton 276

Dalton R 189

Dameshek W 130, 210, 231, 318

Dammin GJ 123, 219

Dausset J 24, 26, 51, 53, 66, 107, 136, 161, 162, 300, 301, 322, 327, 355, 359, 360, 361, 363-366, 368, 369, 481, 483-485, 487, 508, 515, 516, 522, 523, 528, 541, 688

David C 30

Davids J 400

Davies 235

Davies DAL 29, 30

Davies L 327

Day R 388

De Bruyere M 342

De Chardin T 11, 13

De la Chapelle A 205, 208

De Meurichy W 344

De Witt C 679, 680

Dealy JB 130, 219

DeBakey M 576, 685

Defendi V 542

DeKoning J 406, 509

Delmonico FL 320

DeLormer A 603

Demant P 28, 30, 31

Dempster WJ 41, 64, 98, 125, 137, 148, 229-231, 233, 310, 353, 587, 590, 639, 640, 678

Denis 51

Derom F 169

Desarmenien 41

Desjardins H 295

Desnick R 460

DeVries MJ 403, 406, 426, 547

DeVries P 422

Dewaele A 344

Dexter M 422, 428

Diamond L 384

Dicke H 601, 603

Dicke K 386, 403, 407, 409, 412, 413, 415, 420, 425

Diener E 304

Dienstag J 320

DiPadua D 327

Dixon F 64, 322, 453, 454

Dobelle W 266

Doll R 649

Donald HP 80

Dong E 435-438, 442-444

Dooren LJ 406, 423, 509

Dossetor JB 293, 294, 299, 300

Dossetor M 300, 305

Doube 681

Downes G 597, 609

Dubelaar 422

Dubernard JM 169

Dubost C 39, 147, 555, 639, 688

Dunea G 251, 258

Dunn D 460

Dunphy B 219, 456

Dunphy JE 587, 590, 592, 597

Dupont 357

Dupont B 488, 523

Dutton RW 542

Earle WR
98
Ebert J
83
Eddington D
266
Eernisse JG
498
Egdahl R
150
Egelandsdal B
361, 369
Egorov I
28, 30
Egorov O
30
Ehrlich P
11
Eichwald EJ
24, 26, 29, 98, 199, 200, 202, 205, 207, 322, 365
Eijsvoogel VP
508, 543
Eiseman B
152
Elberg SS
356
Eliason J
420
Elion T
130, 137, 192, 233, 239, 318, 339
Ellis H
234
Ende N
483
Epstein R
384
Erben
250
Ettenger R
525
Evans D
234
Ewing M
639, 641, 643
Fabre J
648, 649, 653
Failor E
23, 29
Farber S
201
Federman D
205
Fefer A
385, 387
Feldman J
453, 454
Fellous M
205
Fenner F
4, 80, 97, 186
Ferrebee J W
189, 358, 360, 381-383
Festenstein H
542
Fey B
39
Figueroa J
251
Finch C
381, 384
Fischer R
84
Fletcher
278
Fliedner T
384, 398, 408-410, 427
Forbes J
645
Ford CE
381, 397, 400
Foster M
80
Franklin E
368
Frantz P
53
Freeman R
311
French M
648
Frerik
426
Friedman E
368
Fritz
251
Fuggle S
653
Fuller T
322
Furth J
202, 203
Gaillard P
202
Garey W
205
Garnier H
164, 235
Garovoy M
526
Gayle
278
Gelin C
666
Gerardi F
327
Gerbode F
437, 440
Gerritsen W
417
Gey G
202
Gianello P
344
Gibson T
3, 124, 185, 188, 229
Gifford R
251
Gil-Vernet
52
Ginn H
271
Ginsberg H
403
Gittes RF
314
Gjertson D
533
Glaser RJ
126, 127
Glassock R
219, 368
Glenn J
486
Goddard DR
86
Goldblatt
257
Goldman L
440
Goldman R
221
Goldstein G
165, 326
Good R
102, 210, 322, 365, 385, 407, 509, 546, 547
Goodman H
328
Goodwin W
49, 52, 132, 155-158, 160, 162, 166, 215, 216, 319, 454, 525, 678
Gorer P
9, 10, 21, 22, 24, 26, 29, 98, 106, 107, 136, 185, 206, 231, 313, 318, 352, 477-480
Gorski R
205
Goru E
26
Goulon
48
Gowans J
312, 317, 622, 624, 649, 650
Gozzo J
625, 626
Grabar P
352
Graff R
29
Graham
688
Graham T
383, 384, 386
Graver B
530
Gray D
652, 653
Gray I
519, 619, 621, 641

Gray JG
481
Greene HSN
185, 201, 203, 352
Greenough W
383
Grillo H
314
Grobstein C
80
Grollman A
247
Gropp A
205
Groth C
147, 168, 169, 353
Grullon J
369
Guiney E
640
Gurin S
86
Gye WE
79
Haas
257
Habib R
67
Hagenbeek T
412, 421, 425-427
Hager T
383
Haldane JBS
7, 311, 312, 477
Haldane JS
312
Hall J
205
Hamburger J
41, 61, 62, 68, 69, 105, 130, 153, 155, 158, 230, 251, 276, 296, 364, 365, 683
Hammond
516
Hansen J
387, 388
Hanto D
460
Hardy JD
604, 685
Hardy M
286, 625, 626
Harkins D
438
Harris N
486, 488
Harrison JH
40, 41, 51, 113, 127, 217-220, 229, 269
Harrison RG
79
Hasek M
29, 82, 100, 106, 206, 209, 365
Haskova V
384
Hasthorpe
424
Hattler B
491
Hauschka T
478
Hayry P
353, 542
Healey W
317
Heidt P
412, 421
Heim L
386
Henderson DA
383
Hendriks
412
Herman E
383
Herrin J
320
Herweijer
422
Heston W
203
Hether
422
Hewitson
572, 574
Hewitt C
251
Higgins GF
26
Hildemann W
29, 84, 85, 107, 313, 322
Hilgert I
30
Hinchy
274
Hirsch J
322
Hirschhorn K
541
Hitchcock
572, 574
Hitchcock C
159, 160
Hitchings G
130, 132, 137, 153, 192, 233, 239, 318, 339, 677
Hitdiys J
233
Hodes RJ
542
Hodges C
219
Hoecker G
26, 365
Hoecker P
384
Hoffmann R
587, 597, 599-601, 603, 604, 609
Holiday M
459
Holman E
136, 353, 440
Holmes J
153
Hood L
211
Hoogerbrugge P
417
Hopewell J
229, 231
Hotchkiss RS
361
Howard J
188
Hraba T
106
Hudgins L
483
Hufnagel C
126
Huggins C
309, 315
Hume D
43, 51, 63, 111, 112, 114-116, 126, 137, 147, 150-152, 154-156, 158, 159, 168, 185, 217, 220, 221, 231, 260, 269-271, 273, 276, 278, 280, 281, 319, 323, 353, 360-362, 368, 461, 483, 541, 568, 577, 639, 641-643, 678, 679
Humphrey J
622
Humphreys GH
316, 318
Hunter J
85, 124
Hurley EJ
442-444
Hurley S
370
Hutchin P
491
Hutchinson I
653
Huxley J
313
Inglis FG
299
Ingram M
384
Isakov N
546
Israels L
384
Ivanzi P
31
Ivy A
203
Iwaki Y
526
Iwasaki Y
164

Jaboulay 49
Jacobsen LO 381, 400
Jacobsen S 266
James K 164, 189
Jamieson N 607
Jeannet M 321, 641
Jeejeebhoy HF 620
Jerne N 322
Johnson A 491
Johnson G 640
Johnson R 149
Jonasson O 166
Jones K 205
Jonker R 422
Josso N 205
Jost A 205
Joysey V 234
Kabat E 318
Kahan BD 147
Kahn RL 352
Kalayoglu M 607, 609
Kalff M 603
Kaliss N 22, 23, 26, 203, 204, 206, 321, 352, 478
Kamada N 235
Kano K 368
Kantrowitz A 576, 686
Kasakura S 383
Kashiwagi N 164
Katkov W 320
Kauffman HM 276
Kaufman J 220, 221
Kaufmann 49
Kaupp HA 149
Kay HEM 384
Kayhoe D 482
Keeler R 605
Kelemen 408, 410
Kelley W 458
Kelly WD 158, 169
Kelton D 26
Kermack K 311
Kestens PJ 341
Keynes R 234
Khastagir 251
Kilbrandom 681
Killmann S 427
Kilner TP 77
Kincaid-Smith P 643
Kiser W 251, 261
Kissmeyer-Nielsen F 297, 301, 484, 488, 492, 523, 642
Klebanof 278
Klein G 365, 485
Klein J 28, 30
Knaan S 417, 418
Knapik S 370
Kohler G 165
Kolff WJ 123, 158, 245, 248, 250, 252, 253, 259, 263, 266, 297, 361, 457, 661, 677, 678, 685, 688
Koller P 399
Koo G 205
Koprowski H 85, 209, 210
Kostakis A 235
Kostyu D 491
Kountz G 588
Kountz S 53, 353, 437, 585, 586, 599, 601, 603
Kovithavongs T 300
Krivit W 460
Kroc R 205
Krohn PL 79, 148, 319
Kuban D 523
Kung P 324
Kuschner M 368
Kuss R 37, 38, 44, 46, 50, 54, 63, 67, 147, 153, 155, 158, 159, 353, 639
Kwan-Gett CS 685, 688
Lacey 652
Lafferty K 545
Lahiri 409
Lajtha L 398, 399, 408, 410
Lalanne CM 64
Lalezari P 508
Lancaster S 489
Lance E 622
Land W 628, 630, 662
Landsteiner E 126
Landsteiner K 11
Latinne D 342, 344
Laufer R 327
Law W 644, 653
Lawler RH 39, 147
Lawrence HS 209, 318, 322, 327, 351, 353, 354, 356, 357, 360, 363, 365, 368, 369, 485
Lawrence W 281
Lazarus R 149
Le Gros Clark W 229
Leadbetter G 320

Leadbetter W
218, 320
Ledney D
403, 404
Lee HM
113, 150, 267, 268, 273, 281, 361, 483, 642
Lee S
648
Leen JP
619
Legrain M
41, 44, 53, 67
Legrand L
361
Lengerova A
27, 29
Levey R
323, 622, 623, 625
Lewis FJ
440
Lewis J
149
Lewis W
80
Lillehei CW
298, 440
Lillehei RC
158, 169, 458
Lillie FR
97, 124, 136
Lim E
533
Lim Y
649
Lipinsky J
320
Lister J
238
Little CC
21, 23, 24, 203
Lochte H
383
Loeb L
136, 185
Loewenthal J
645
Logan A
193
Longmire WP
98, 151, 217, 218, 276, 353, 513, 515
Loofborough J
381
Lorenz E
381, 400
Loutit J
103, 397
Lowenberg R
412, 420
Lower RR
132, 168, 274, 276, 281, 436, 438, 439, 441-444, 567, 568, 685
Ludford
477
Luke JC
295
Lumsden T
477
Lysenko
106
Maat B
409
Mack W
370
MacKay I
645
MacKenzie I
327
MacKinnon KJ
295, 299
MacLean LD
296, 299
MacLeod C
368
MacQueen M
486
Main
381
Maingot R
185
Maki T
285, 625, 627
Manley J
102
Mann FC
125
Mannick J
150, 271, 358, 382, 383, 624
Marchioro T
154, 156, 157, 678
Marshak R
86
Marshall V
643
Martelli
416
Martens ACM
426
Martin D
158, 220, 519
Martinez C
102
Mathe G
41, 49, 365, 384, 386, 398, 403, 405, 406
Mathe J
485
Mauer M
459
Maumenee AE
352
Maxwell M
219
May R
603
McCarthy M
357
McClelland J
516, 648
McClusky R
368
McCracken
557
McCulloch EA
402
McDevitt H
29, 618, 645
McGovern J
315
McKenzie I
25, 30
McKenzie J
649, 653
McLaren A
101
McLaughlin
205
McMichael A
653
Medawar J
3, 5, 7, 10, 11, 14, 15, 104, 313, 463, 514
Medawar P
1-3, 24, 43, 68, 76-82, 85, 95-107, 124, 130, 133, 136, 148, 164, 185, 186-188, 202, 204, 206, 229, 231, 233, 234, 238, 276, 282, 297, 309-313, 315, 316, 319, 322, 323, 327, 352, 353, 360, 364, 365, 381, 453, 463, 477-479, 481, 485, 499-501, 513-515, 517, 541, 618, 622, 623, 625, 639, 643, 648, 650, 663, 665
Mellanby E
312
Mellinkoff S
515
Meo T
543
Merchav S
424
Merkel FK
166
Merrill JP
40, 41, 48, 50, 51, 64-66, 117, 126, 127, 137, 147, 152, 158, 217, 219, 229, 249, 367, 384, 624
Mervart H
299
Metcalf D
409-411, 420, 422
Metchnikoff E
164, 165, 619
Meuwissen H
547
Michael A
459

Michie D
188
Michon L
63
Michurin
106
Mickey D
101
Mickey MR
530
Middleton M
192
Miescher
508
Miescher P
368
Mikulska ZB
29, 478
Miles A
477
Milgrom F
368
Miller A
369
Miller D
127
Miller JFAP
206, 317, 406, 620, 646
Miller RF
409
Millington
276
Milstein C
165
Mirsky IA
147
Mitchison A
7, 9, 95, 106, 231, 312, 479
Mittal KK
517
Mollaret
48, 340
Moller E
107
Moller G
107, 209
Molomut N
23, 26
Monaco A
164, 208, 269, 320, 323, 364, 615, 616, 623, 624, 627, 629, 630
Monaghan ED
299
Monchik GJ
151, 327
Montagnier L
424
Moor-Jankowsky J
680
Moore F
113, 123, 126, 130, 132, 137, 147, 149-152, 218, 219, 230, 233-235, 280, 320, 321, 339, 353, 368, 591, 624, 678, 684
Moore G
165
Morelle J
339, 340
Morgen RO
295
Moriau M
342
Morris PJ
276, 284, 353, 361, 364, 516, 525, 637, 638, 644, 646, 647, 651, 654
Mottram P
649, 653
Moulopoulos S
266
Mulder D
422
Mulholland JH
368
Muller U
205
Muller-Berat N
412
Murphy JB
185
Murray J
40, 41, 47, 54, 63, 121, 122, 125, 126, 131, 132, 147, 148, 151, 152, 154, 155, 158, 191-193, 210, 217-219, 229, 230, 233, 234, 296, 318, 319, 321, 339, 353, 365, 367, 381, 541, 617, 624, 639, 645, 677, 678, 683, 684
Najarian J
165, 282, 342, 353, 451, 452, 455, 457, 461, 463, 464, 590, 597, 599, 621
Nakamoto S
245, 246, 250, 251, 253, 678
Nakeff
420
Nathan D
384
Nathenson SG
29
Nedey R
41
Neiman P
385, 387
Nelson S
640
Nevins T
459
New M
205
Newth D
311
Nigg C
356
Nolan B
193
Nooter
424
Nose Y
246, 250, 262, 685
Nossal G
365, 641, 643
Nowell PC
397, 400, 402
O'Connor H
327
O'Donovan T
572
O'Hara P
491
O'Hare J
123
O'Kunewick JP
386
O'Reilly R
415, 425
Ochiai
285
Oeconomos N
39, 63
Oh J
297
Ohno S
205, 208
Ohta
287
Opelz G
53, 189, 530, 649
Ormai S
426
Ota K
604
Oudin J
515
Oudot J
39, 63
Ovary Z
368
Overman J
403, 482
Owen D
650
Owen J
106
Owen R
4, 43, 65, 80, 81, 84, 97, 100, 102, 103, 105-107, 124, 136, 206, 209, 485, 514
Oyer P
444
Padgett E
124
Page I
246, 247
Page L
320
Pappenheimer AM
368, 619

Park MS 524

Parkes AS 79

Patel R 520, 525

Payne R 385, 456, 481, 508, 516, 522, 541

Pazderka F 299

Peacock JH 164

Peart S 234

Peer L 208

Pelliniemi L 205

Penn I 161, 282, 285

Perkins H 456

Perper R 454, 457

Perrin 51

Persijn G 664

Peters R 397

Petrov R 403, 404

Phelps HJ 477

Philips D 650

Pichlmayr R 353, 628, 659, 660, 662, 664

Pierce G 361

Pierce J 281, 361

Pirsch J 609

Plate J 489

Platt J 343

Plimpton CH 591

Ploeg R 607

Ploemacher R 428

Pluznik D 409, 411, 420

Poisson J 41, 46-49, 51, 53, 155, 159, 160

Popper K 5

Porter 257

Porter K 80, 234

Porter KA 158-160, 162-164, 170, 230, 231

Porter R 649, 650, 653

Posner 286

Potter D 459

Poutasse E 247, 249, 251

Prehn RT 203, 381, 479

Prentice HG 412

Pressman D 352

Pullis C 369

Purdy A 440

Putnam CW 169

Pyke D 12

Quel A 369

Quinby WC 125

Raisbeck AP 361, 369

Ramseier H 85

Rand J 253

Rantzen E 235

Rapaport F 161, 162, 210, 281, 284, 317, 327, 349, 350, 359, 364, 365, 485, 486, 528, 688

Rasmussen AF 515

Rasmussen B 485

Ravdin IS 86

Ravitch MM 356

Rayfield L 102

Reemtsma K 49, 52, 159, 553-555, 557, 679, 681, 684

Reeve CE 299

Reif AE 30, 478

Reilly B 370

Reiman S 83

Reinsmoen N 546

Reisner Y 415

Reitz B 444

Revillard JP 681-683

Revillard ML 682

Reynolds J 79

Richards V 438

Riddell A 310

Rittenbury M 274

Roach J 653

Robinson RR 486

Robinson S 440

Robinson W 409, 411

Roehl 53

Rogers B 203, 206, 317, 485

Rohloff W 259

Rolley 276

Rombouts JJ 341

Roopenian D 28, 29, 546

Rosenbaum 251

Rosenthal T 221

Roser BJ 235

Ross B 426

Ross F 486

Ross J 191

Rougelle J 39

Rous P 80, 315

Rowntree T 640

Rubenstein P 384

Rubin N 320

Rubin R 319, 320

Rudolf L 483

Ruskiewicz M 97

Russell P 84, 107, 151, 164, 188, 287, 307, 308, 325, 327, 353, 364, 365, 384, 481, 619,

621, 623, 624, 640, 641
Russell W 23
Sachs 420
Sachs D 327
Sachs J 619
Sacks J 276
Sacks JH 323
Sahler O 383
Salvatierra O 285, 353, 365, 464, 601
Sanfilippo F 502, 654
Santos G 384, 386, 405
Sargent A 299
Schaefer U 420
Schalm SW 166
Schechtman A 513
Schendel D 543, 545
Schippers A 501
Schlaut J 300
Schlegel 557
Schmittdiel E 665
Schribner B 124
Schrire V 569, 571
Schroeder M 299
Schulgen C 662
Schulman B 533
Schultz 426
Schwartz R 132, 210, 231, 318
Schwartzenberg L 41
Scott WW 217
Scribner B 361
Seigler HF 486
Selden R 328
Seldin D 87
Sensenbrenner L 386
Senzig K 604
Servelle M 39, 147, 639
Seto D 251
Shackman R 47, 51, 53, 158, 159, 639, 640
Shaftan G 590
Shanfield 278
Sheer M 203
Sheil R 353, 366, 645
Sheldon W 210
Sherlock JS 370
Sherlock S 304
Shibagaki M 251
Shield R 284
Shons A 457
Shortman K 409
Shreffler DC 26, 29, 542, 543
Shreiner G 683
Shull SF 30
Shulman 522
Shumway N 132, 133, 137, 149, 168, 169, 353, 435-444, 457, 567, 685, 686
Siegler HF 483
Silmser CR 29, 207-209
Silvers WK 83, 85, 322
Simmons R 165, 316, 460, 461, 620
Simonsen M 103, 125, 137, 229, 230, 234, 310, 352, 541
Simpson J 205
Sinclair NR 299
Singal DP 527
Skamene A 327
Skamene E 327
Skoskiewicz M 326, 328
Slapak 286
Slome D 230
Smellie A 639-641
Smith CE 356
Smith JM 311
Smith P 26, 29
Smith RC 533
Smithers 230
Snell G 9, 19, 20, 26, 28, 31, 136, 203, 204, 321, 477, 478, 542
Snell ME 166
Snell R 26, 28
Sokal G 341
Sokoloff L 368
Solliday S 542
Sollinger H 546, 607, 609
Sondel P 545
Sonneveld 426
Southard J 604, 609
Sparrow E 234, 310-312, 314, 478
Speck 509
Spencer FC 360
Spoljar M 205
Springer G 357
Spurway H 311, 312
Squifflet JP 342, 345
Stankovic V 403
Starzl TE 47, 49, 51, 52, 132, 137, 145, 146, 156, 188, 193, 205, 206, 235, 297, 319, 323, 341, 353, 361, 363, 364, 368, 456, 457, 512, 526, 568, 607, 609, 620-622, 665, 677-679, 681, 683-685

Steeper K
599-601
Stefanini P
680, 682
Steinmueller D
208
Stenger K
327
Stephenson M
369
Stetson A
368, 482
Stewart B
251
Stickel D
483, 486
Stiller C
627
Stimpfling J
23, 29, 205, 206, 542
Stinson EB
439, 444
Stocker J
644
Stofer R
440, 442
Stohlman F
384
Stokdijk W
422
Stone FL
482
Stone W
365
Stonington O
156
Storb R
385, 387, 415
Stormont C
485
Stowell RE
203
Straffon R
251
Streilein JW
85
Strominger J
529
Stuart
203
Stuart F
648
Stulting D
491
Sullivan K
489
Sulzberger MB
352
Sundberg R
607
Surman O
320
Sutherland D
169, 283, 342, 459
Svedmyr EAF
542
Svejgaard A
301
Swisher S
384
Tagnon H
398
Takagi
283
Takemoto S
532
Taub R
622, 623
Taylor B
27, 29
Taylor H
648
Teinturier J
39
Terasaki PI
51, 66, 95, 107, 155, 159, 161-163, 166, 189, 217, 220, 221, 274, 276, 285, 301, 302, 313, 322, 364, 367, 453,456, 480, 481, 483, 511, 512, 522, 523, 603, 641-643, 649, 653, 654, 688
Terblanche J
235
Terpstra J
603
Thibault P
53
Thomas ED
189, 358, 379, 380, 382, 384, 386-389, 405
Thomas F
362
Thomas J
278, 362, 625
Thomas L
11, 209, 318, 356, 357, 360, 367, 368
Thorbecke J
318
Thorn G
123, 124, 126, 210
Tidow G
662, 663
Till JE
386, 402
Tillet WS
356
Tilliakainen A
488
Tilney NL
137
Ting A
525, 644, 645, 653
Tocantins L
384
Todd J
653
Toolan HW
352
Topaz S
266
Traeger
51, 165
Trentin JJ
386, 402
Tridente G
403
Trinkaus JP
80
Truman C
599, 601
Trunkey D
603
Tubiana M
41, 64
Uhr J
368
Uphoff D
381, 383
Valerio D
417
Van Arsdel P
322
Van Bekkum D
365, 384, 386, 395, 396, 404, 405, 408, 411, 413, 414, 416, 418, 419, 421, 425, 427, 429-431, 485, 547, 622, 625
Van de Engh G
421
Van de Putte L
603
Van Dekken H
422
Van den Engh G
422, 425
Van der Waay D
412
Van Dura D
250
Van Es M
419
Van Hooff JP
286, 502
Van Hooft JIM
409
Van Leeuwen A
498, 501
Van Loghem
508
Van Niekerk W
205
Van Noord MJ
409
Van Putten LM
403
Van Rood JJ
26, 51, 189, 192, 286, 325, 341, 365, 385, 403, 412, 456, 479-481, 483, 497, 498, 508, 509, 516, 522, 523, 541, 547, 641, 664, 688
Vaughan H
653

Vaysse J
41, 63
Vernier R
459
Versaci
251
Visser J
422, 423
Vlahakes G
320
Vlahovic S
384
Von Kaulla K
155
Voronoff S
39
Voronoy YY
147
Vos O
400, 422
Vossen J
412, 423
Vourc'h
41
Vriesendorp HM
415
Wachtel G
205
Wachtel S
205
Waddell WR
152, 155, 156, 158, 319, 678
Wade J
299
Wagemaker G
415, 420
Wahlberg J
607
Wain J
320
Waksman B
164, 322, 617
Waksman BH
619
Walford R
481, 516
Wall WJ
166
Wallace-Toolan H
203
Walsh
51, 53
Walter CW
123
Waltzer WC
362
Wangensteen O
440
Ward F
483, 489, 491
Washkansky L
569, 575, 686
Watschinger B
250
Watson
230, 231
Watson DMS
7, 96, 311
Watson JD
6, 13
Watt J
189
Weaver JM
479
Webb W
442
Webster E
315
Wee SL
546
Weiss P
80
Weiss S
123
Weissman I
207, 209-211, 423
Welch C
640
Welch CS
167
Wells GP
311
Wesson LG
304
Weyzen W
400
White D
235
Widmer M
543, 546
Wielenga J
417
Wilder LD
277
Williams GM
270, 274, 276, 361, 483, 641-643
Williams K
653
Williams N
422
Williams R
235, 384, 385
Williamson
39
Williamson CS
125
Wilson JW
204, 205
Wilson RE
137
Winn H
26, 30, 313, 321, 322, 325-327, 491
Witebsky E
368
Wolf J
281, 285
Wolf U
205
Wolfe W
361
Wonigeit K
663, 667
Wood K
653
Wood M
208, 314, 316, 619, 625-627
Wood R
653
Woodbury M
491
Woodger JH
78
Woodruff H
171, 190
Woodruff M
51, 53, 124, 158, 164, 171, 183, 184, 190, 218, 231, 276, 322, 325, 353, 364, 365, 384, 501, 604, 619, 622, 623, 663, 665, 678, 679, 681, 683
Wright P
205
Young H
320
Young JZ
76
Yunis E
488, 489, 508, 541
Zamecnik PC
314
Zenker R
661, 663
Zimmerman P
235
Zinkernagel RM
29
Zipori D
424
Zir K
546
Zisman A
369
Zmijewski C
487, 491
Zoschke D
542
Zukoski CF
130, 150, 169, 231, 269, 684